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Toward a Symphony of Reactivity: Cascades Involving Catalysis and Sigmatropic Rearrangements

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Abstract

Catalysis and synthesis are intimately linked in modern organic chemistry. The synthesis of complex molecules is an ever evolving area of science. In many regards, the inherent beauty associated with a synthetic sequence can be linked to a certain combination of the creativity with which a sequence is designed and the overall efficiency with which the ultimate process is performed. In synthesis, as in other endeavors, beauty is very much in the eyes of the beholder.^[**] It is with this in mind that we will attempt to review an area of synthesis that has fascinated us and that we find extraordinarily beautiful, namely the combination of catalysis and sigmatropic rearrangements in consecutive and cascade sequences.

Keywords

homogeneous catalysis; sigmatropic reactions; tandem reactions

1. Introduction

The development of tandem processes has had a profound impact on organic synthesis and synthetic planning. Combining multiple reactions in a series affords highly functionalized products with minimal handling. Likewise, with the growing body of catalytic reactions and their importance for the synthesis of asymmetric intermediates, it is understandable that catalysis is a broad area of focus in the 21st century. Although the coupling of highly

^{**}Sometimes the assessment of beauty is nearly unanimous. The first four notes of Beethoven's 5th Symphony (Symphony No.5 in C minor, Op.67) represent perhaps the most well-known and popular motif in classical music. The orchestral score is shown in the background of the cover graphic. Accessed March 20, 2013 from http://imslp.org/wiki/Symphony_No.5,_Op.67_%28Beethoven,_Ludwig_van%29.

efficient catalytic transformations to other processes, particularly those that are thermally mediated, could be expected to be a key motif for accessing highly complicated substances with exquisite control and efficiency, this line of research is in its relative infancy. In this review, we cover cascade reactivity in the context of catalytic transformations that are coupled to bond rearrangements, specifically sigmatropic processes. We will discuss ensembles of reactions involving the combination of catalysis and sigmatropic rearrangements, including Claisen, Cope, [2,3], [1,2], [1,3], and [1,5] rearrangements. It is our aim that this analysis will afford future researchers the opportunity to build on such cascades for further development of more selective and powerful transformations.

1.1. Defining and Classifying Cascades

1.1.1. Defining Tandem Reactions and Reaction Ensembles—Chemical reactivity is difficult to define and classify. Classifications of tandem reactions become even more cumbersome because of the fact that nearly every chemical reaction comprises multiple elementary steps. Such combinations of elementary steps are generally not categorized as tandem or cascade reactions, and are simply referred to as the mechanism of a particular process. Alternatively, combining multiple reactions leads to the concept of tandem reactivity. For our purposes, we will adhere to the definitions put forth by Tietze, such as the overarching “sequential” or “one-pot” reaction.^[1] This includes “domino” reactions (also known as tandem or cascade) whereby “subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.” “Consecutive” processes would be ones where additional reagents are added without isolation of the first formed product. One caveat that we would like to add to the literature involves more precisely defining these processes based on the number of discrete reactions involved. In fact, the need for such a classification system arose in one of our own publications involving a cascade of three reactions. We initially named this a triple tandem reaction. This descriptor unfortunately implies three sequential tandem events, or six reactions in total, which is incorrect.

After a number of discussions with one of our esteemed colleagues, the now late Professor Nelson Leonard, we developed a more precise terminology. We propose to use the descriptors duet, trio, quartet, quintet, etc. for defining tandem events involving 2, 3, 4, 5, etc. reactions in a reaction ensemble. Ultimately, this naming system leads one to envision entire symphonies of reactions occurring in controlled, multi-reaction cascades. Moreover, the beauty and creativity associated with music allows one to draw a more subtle analogy between music and synthesis as well as art and science. The classification herein is in contrast to “concerto catalysis,” which seeks to improve traditional metallic catalysts by uniting them with all scales of catalytic assemblies, from large biological macromolecules to small molecules, an endeavor which would require and encourage cross-disciplinary thinking.^[2] Both concepts appeal to the musical sense of orchestration in chemical synthesis, and illustrate the goal of chemists to attain more exquisite control over chemical processes.

1.1.2. Defining Catalysis—Chemical catalysis can be defined as the utilization of a reagent for the purpose of enhancing the rate of a reaction without altering the makeup of

the reagent. This definition is sufficiently broad to encompass catalysts used in both small (substoichiometric) and large (stoichiometric and superstoichiometric) quantities as well as relatively complicated ($[\text{Ir}(\text{PCy}_3)_3]^+\text{BPh}_4^-$) and simple (H^+) catalysts. Because of the potentially huge numbers of reactions that could fall under this definition, we have necessarily been somewhat selective in terms of what is included in this review. This is not a comprehensive review; rather it is our intention to provide illustrative examples that may ultimately provide the reader with not only breadth in the area, but enough depth to push the science beyond what is currently possible.

1.1.3. Defining Sigmatropic Rearrangements—Woodward and Hoffmann defined a sigmatropic rearrangement of order $[i,j]$ to be “the migration of a σ bond, flanked by one or more π -electron systems, to a new position whose termini are $i-1$ and $j-1$ atoms removed from the original bonded loci, in an uncatalyzed, intramolecular process.”^[3] For the purposes of this review, we will use a somewhat more loose definition based solely on the transformation and the bonds formed and broken. The strict uncatalyzed, unimolecular, and concerted definition of Woodward and Hoffmann are simply too constricting for this topic. Moreover, we have deliberately limited this review to sigmatropic processes and not attempted to review all pericyclic processes involved in catalyzed tandem reactions. There are excellent reviews written specifically on topics dealing broadly with tandem and/or pericyclic reactions.^[4] It was our belief that including such areas in the review would be an unnecessary repetition of these topics, and the examples involving sigmatropic rearrangements (of which there are significantly fewer) would not stand out. By incorporating these two relatively simple strategies (catalysis and sigma-tropic rearrangements) in cascade sequences, an incredible diversity of transformations is possible. As a result, the material described herein does not always fall neatly into subcategories, and multiple transformations presented in one section are connected to transformations presented elsewhere. Figure 1 provides a visual overview to our organization; reactions are grouped according to major “themes” to the extent that we could find them. In particular, incorporation of the Claisen rearrangement into tandem sequences showed the broadest versatility and diversity, a clear outcome of the many known variants of the Claisen rearrangement. Rather than being a drawback, we hope the broad coverage will inspire further discovery by highlighting the multiple connections possible between various methodologies, and providing a framework for thinking about new ways to combine multiple processes into one.

1.1.4. Classification: Duets, Trios, Quartets, and Higher—The review is primarily classified by the type of sigma-tropic process. Within each group, the examples are subdivided by the first sigmatropic rearrangement that occurs in that cascade. Although it would be illustrative to organize according to increasing complexity, we found the discussions to be too fragmented. Within each section, reactions are thus named according to the number of discrete events occurring in a cascade sequence (i.e. duets (2), trios (3), quartets (4), etc.). The duet constitutes the simplest musical group beyond a soloist, but allows for nearly unlimited binary combinations of musicians. Likewise a chemical duet is the simplest, and by far the most common, type of tandem reaction. As in music, the chemical interplay of the two voices of reactivity leads to a combination that is greater than

the sum of the individuals. Even more impressive is the choreographing of additional chemical processes, each with their own selectivity, into trios and quartets.

In many cases, particularly when mechanistic information is deficient, it can be difficult to quantify the discrete number of steps. A number of judgements are required. For example, do tautomerizations count as discrete steps? Do reversible processes to form intermediates at low concentration merit tallying? We have attempted to make those judgments according to context and have used our best discretion when selecting the most noteworthy examples. The inclusion of reactions that are chemically catalytic without being operationally catalytic, or those that are consecutive (multiple reagent additions) rather than the more elegant and advantageous tandem, is intended to reveal both the advances and shortcomings of attempts to incorporate multiple (catalytic) transformations under one given set of conditions (often not yet possible). The true testament to our ability to “orchestrate” will be to have all musical partners present at the outset – with all the requirements for reagent selectivity and compatibility that would entail.^[*]

2. [3,3]-Sigmatropic Rearrangements

2.1. Cope Rearrangement

Although it is the prototypical example of a [3,3]-sigma-tropic rearrangement, the all-carbon Cope rearrangement was discovered after its oxygenated counterpart, the Claisen rearrangement. Found by Cope in 1940^[5] and subsequently developed further, the simplest example (the rearrangement of 1,5-cyclohexadiene, **1**) is a degenerate reversible process that can be studied only by labelling and/or substitution experiments. The reversibility of the Cope rearrangement presents a challenge for its use in a synthetic or practical sense, as well as for the development of asymmetric variants.^[6] Different strategies have been employed to drive the rearrangement toward a desired product. For example, the thermal rearrangement disclosed in Cope's original report (**2**→**3**, Scheme 1), involves a significant thermodynamic driving force from the introduction of conjugative stabilization. Introduction of aromaticity either directly or through tautomerization is another way to favor Cope-rearrangement products.^[7] Two other widely used strategies are the strain-release Cope and oxy-Cope rearrangements, each of which are discussed further below. A number of good reviews of catalysis in the Cope and Claisen rearrangements have been published.^[8] Most of the examples included herein do not necessarily involve catalysis of the Cope rearrangement step.

2.1.1. Strain-Release Cope Rearrangement—Introduction of a cyclopropane or cyclobutane is a very commonly used strategy for rendering a Cope rearrangement

^{*}We thank one referee both for his or her close examination of our manuscript, but also for their careful consideration of our choice of language. We appreciate the insight that in musical ensembles, each “member usually contributes their sound at an identical moment in time, not one after the other. In contrast, a 1-pot reaction sequence is composed of a series of transformations, which occur consecutively.” We believe that part of the success of these reactions is the requisite compatibility and selectivity of multiple reagents and functionalities. Part of group music, for sure, is “waiting your turn.” At times an individual musician must remain silent; similarly, the success of these reactions relies on the minimization of other reaction pathways. Although our duet, trio, etc. terminology counts reaction steps as ensemble members (rather than the acting reagents themselves), we have chosen to stay faithful to our original conversation with Nelson Leonard. We invite the community to continue discussing the best way to characterize these reaction cascades.

irreversible. Cis-divinyl cyclopropanes cannot often be isolated because they rearrange too quickly, although mechanistic studies by Brown et al. were successful in measuring the free energy of activation for the rearrangement of the parent divinyl cyclopropane in CFCl_3 ($\Delta G^\ddagger = 20.6 \text{ kcal mol}^{-1}$, for example, $t_{1/2} = 90 \text{ s}$ at 35°C).^[9] The facility with which the Cope rearrangement occurs in these systems makes it a prime candidate for incorporation into tandem reaction sequences.

Ever since Davies and co-workers^[10] first reported the rhodium-catalyzed cyclopropanation/Cope rearrangement duet, the strategy has been used to great effect in a number of total syntheses to generate seven-membered rings. The use of enantiomerically pure rhodium catalysts that render the reaction asymmetric has been of particular impact. To date, these are the most prevalent examples of catalyst control in asymmetric all-carbon Cope rearrangements.^[6b,11] A recent example from the Davies group in the context of natural product total synthesis is shown in Scheme 2. Asymmetric cyclopropanation of triene **4** followed by Cope rearrangement, with transfer of chirality generated cycloheptadiene **7** in good yield and high enantiomeric excess. This intermediate was further elaborated to the natural product (–)-5-*epivibsanin*, **8**.^[10c]

One of the authors of this review employed an enantio-selective cyclopropanation/Cope rearrangement duet in a “parallel kinetic resolution” to prepare enantiomerically enriched diastereomers from racemic starting material (Scheme 3).^[12] When a racemic mixture of diene **10** was treated with a vinyl diazoester and an enantiomerically pure dirhodium tetraproline catalyst, diastereomeric cycloheptadienes **13** and **14** were isolated as a 1:1 mixture, each with enantiomeric ratios of 88:12. The moderate e.r. values indicate imperfect facial selectivity of the catalyst. The resolution of racemic **10** could thus be used to prepare tricyclic cores of the cyanthiwigin and the cyathane diterpenes, each enriched in the naturally occurring enantiomer.

Padwa and co-workers explored extensively the isomerization of α -diazo ketones that bear tethered alkyne units (Scheme 4).^[13] Thus, diazoketone **17** isomerized to rhodium carbenoid **18** upon treatment with catalytic rhodium(II) mandelate. A cyclopropanation occurs with the closer of two double bonds. The *E* configuration is necessary, as it alone can furnish the reactive *cis*-divinyl cyclopropane **19**. Cope rearrangement terminated the reaction trio to generate cycloheptadiene **20**.

Montgomery and Ni showed that nickel can catalyze the coupling of enynes with diazocompounds in a related enyne cyclization reaction (Scheme 5).^[14] The details of the mechanism are not known, but model and mechanistic studies support the intermediacy of cyclopropanes such as **24**. Without a clear mechanistic understanding of the process it is difficult to characterize according to the number of reactions, however, prior experimental observation and understanding is most consistent with an alkyne metathesis/cyclopropanation/Cope rearrangement trio.

Tandem cyclopropanation/Cope rearrangement sequences have relied on other transformations beyond [2+1] addition of carbenes to alkenes. Enyne isomerizations with electrophilic metal catalysts can also be used for the *in situ* generation of divinyl

cyclopropanes (Scheme 6).^[15] For example, treatment of diyne **26** with catalytic PtCl_2 led to isolation of the bicyclic cycloheptadiene **28**,^[15a] while treatment of trienyne **29** with catalytic $[\text{W}(\text{CO})_6]$ led to isolation of bicyclic cycloheptadiene **31**.^[15b]

The mechanistic details of the two reactions may diverge slightly, but according to current thinking, each process is initiated by electrophilic activation of the alkyne followed by nucleophilic attack of the pendant alkene (**A**, Scheme 7).^[16] Nucleophilic closure by vinyl metal species **B** can then be envisioned to generate the metal carbene **C**. Hydride shift and loss of metal would then lead to cyclopropane **D**. Cope rearrangement can feasibly occur at this stage. In the case of platinum catalysis, divinyl cyclopropane intermediates can be isolated and have been shown to undergo the postulated Cope rearrangement under thermal conditions, suggesting that metal loss is fast in **C**.^[15a] Intermediates were not isolated in the tungsten-mediated reaction, thus preventing conclusions about when demetallation occurs. The nature of the intermediates shown in Scheme 7 has been the subject of a fascinating discussion along the lines of the historical debate regarding non-classical ion intermediates.^[17]

Two authors of this review expanded the strain-release Cope rearrangement to ketene substrates and developed a Wolff/Cope rearrangement duet.^[18] Sonication of diazo ketone **32** with a catalytic amount of AgOBz and a stoichiometric amount of Et_3N at 45°C led to the desired cycloheptadienone **34** in excellent yield (Scheme 8). Under photo-lytic conditions, the success of the reaction was mixed. Prolonged exposure to light ultimately led to vinyl cyclopentenone **35**. The intermediacy of **34** was confirmed and suggests a subsequent Norrish type **I** fragmentation/recombination as the final step in a Wolff/Cope/1,3-acyl-shift rearrangement trio.

The diminished ring strain in cyclobutanes, compared to cyclopropanes, makes them less reactive but competent substrates for strain-release Cope rearrangements. In the synthesis of the sesquiterpene lactone (+)-asteriscanolide, Snapper and co-workers utilized a cyclobutene ring-opening metathesis/Cope rearrangement duet (Scheme 9).^[19] Although precedent was poor for selective ring-opening metathesis of a strained trisubstituted olefin, treatment of olefin **36** with Grubbs II catalyst under optimized conditions produced cyclooctadiene **38** in excellent yield. In an earlier report, related divinyl cyclobutanes underwent Cope rearrangement only at significantly higher temperatures (200°C). The lower propensity of those substrates to undergo a Cope rearrangement was attributed to substitution at C8, which would disfavor the required parallel arrangement of the two vinyl groups, as in **37**.

Kanematsu and co-workers reported a [2+2] cycloaddition/[3,3] rearrangement sequence of an allenyl ether, which constituted a unique example of the cyclobutane strain-release Cope rearrangement (Scheme 10).^[20] The transformation was initiated by base-catalyzed isomerization of enantioenriched propargyl ether **40** to allenyl ether **41**, which could then engage in a [2+2] cycloaddition. The resultant methylene cyclobutane **42** subsequently underwent Cope rearrangement to generate cyclic ether **43**, a potential precursor to taxane derivatives, in quantitative yield.

2.1.2. Oxy-Cope Rearrangements—In 1964, Jones and Berson demonstrated that particular Cope rearrangement products could be favored by incorporating an oxygen substituent at position 1 (Scheme 1).^[21] Such substrates did not only rearrange “irreversibly” as a result of keto–enol tautomerization, but a kinetic effect was also observed.^[21b] Furthermore, Evans found that rate enhancements were even more significant for anionic alkoxides.^[21c]

Under thermal conditions, tandem pericyclic processes were combined with oxy-Cope rearrangements in complex cascade sequences to great success.^[22] Although a deprotonation would fit within the concept of catalysis, even if the base were used stoichiometrically, we have excluded clearly irreversible examples that utilize bases (e.g. NaH, *n*BuLi), unless such bases are used substoichiometrically. We use a similar constraint to limit the number of examples discussed throughout this review.

The anionic oxy-Cope reaction was first invoked to explain a base-catalyzed dienol rearrangement that could also be explained by a fragmentation–recombination process, specifically a retro-aldol/Michael addition.^[8] For example, Tice and Heathcock reported divergent base-mediated rearrangements of enone **44** (Scheme 11).^[23] With KOH in aqueous methanol, dicarbonyl compound **47** was isolated. With excess KH in THF, dicarbonyl compound **51** was isolated. If a catalytic amount of KH was used, both compounds were isolated in a 1:1 ratio. Both rearrangements were proposed to proceed by retro-aldol reaction to provide enolate **45**. Cyclization could then produce epimeric alkoxide **46** and isomeric alkoxide **48**, which are both prone to undergo oxy-Cope rearrangement. In the case of **46**, enolate protonation terminated the base-catalyzed rearrangement trio to give bicycle **47**. In the case of **48**, the resultant enolate underwent isomerization and Michael addition to form **51**, thus terminating a rearrangement quartet. As mentioned above, such rearrangements need not necessarily invoke an anionic oxy-Cope reaction; direct Michael reactions of **45** constitute a similarly plausible mechanism. We include these reactions in the current review with that caveat.

Another example of a similar catalyzed tandem anionic oxy-Cope rearrangement was reported by Rajagopalan et al. and involved allenic system **52**, a previously unexplored type of substrate for the anionic oxy-Cope reaction (Scheme 12).^[24] Treatment with a substoichiometric amount of sodium ethoxide gave solely the product of anionic oxy-Cope rearrangement, dienone **53**, which formed aldol product **54** upon purification on alumina. Use of a stoichiometric amount of base effected the tandem sequence, oxy-Cope rearrangement and transannular cyclization, to give the bicyclic exo-methylene compound **54**. The allenic oxy-Cope systems were shown to react faster than simple vinyl counterparts; this was attributed to allenic strain, which reduces the strength of the π bond involved in the rearrangement.

In the course of synthetic studies toward the sesquiterpene gnididione, Jacobi and co-workers observed a duet rearrangement/spirocyclization of diynyl carbinols (Scheme 13).^[25] The sequence was initiated by thermal oxy-Cope rearrangement to enynone **55**. *tert*-Butyl catechol (TBC) then catalyzed a radical cyclization to form cyclopentenone **57**. Mechanistic studies supported cyclization following single-electron reduction of the enol tautomer of **56**.

In their work on the preparation of polycyclic structures, Huq and co-workers observed a unique dianionic aromatic oxy-Cope rearrangement trio (Scheme 14).^[26] This was the first report of a dianionic oxy-Cope rearrangement engaging two benzene π bonds as part of a 1,5-hexadiene system.

Although pentacyclic diols, such as **61**, were the expected products, in the case of **58** an unexpected rearrangement trio also occurred. The dianionic oxy-Cope rearrangement led to dienolate **60**, which then underwent single tautomerization, partial proton quenching, and aldol cyclization to give hexacycle **62**. Air oxidation rearomatized one of the phenyl rings to provide **63** in good yield.

In a very elegant use of strain release in a tandem oxy-Cope sequence, Leighton and co-workers developed a method that allows the rapid preparation of the core of phomoidrides, a series of compounds that are squalene synthase and Ras farnesyl transferase inhibitors.^[27] Originally discovered by Pfizer, they are also known as CP molecules. Although there was good precedent for an originally proposed simple anionic oxy-Cope approach, the harsh reaction conditions indicated an unfavorable process that was highly sensitive to even small changes in substrate structure. In order to promote the rearrangement, they decided to introduce an additional strain-inducing feature.

Specifically, an oxy-Cope precursor that already contained the pseudoester ring system of **67** was proposed to have a strained and twisted *exo*-methylene group more prone to engage in a [3,3] rearrangement (Scheme 15). To generate such a strained tricyclic system, they envisioned a novel carbonylation reaction starting from enol triflate **64**. In practice, carbonylation with $[\text{Pd}(\text{PPh}_3)_4]$ gave lactone **67** in good yield. The reaction was proposed to proceed by oxidative addition and CO insertion followed by intramolecular trapping of putative palladium-acyl **65** by the pendant alcohol. Studies on a model system showed that either triflate stereoisomer could be used, implicating a palladium-mediated isomerization. The high complexity of this process was thus more remarkable by potentially being stereoconvergent.

Bode and co-workers reported an asymmetric annulation that was catalyzed by an N-heterocyclic carbene (NHC) and proposed to proceed through a unique oxy-Cope rearrangement (Scheme 16).^[28a] The proposed mechanism involves a crossed benzoin reaction between cinnamaldehyde (**70**) and conjugated ester **69** to generate alkoxide **71**, which is poised for a [3,3] rearrangement. Tautomerization of enol **72** followed by aldol addition would then generate isomeric alkoxide **73**. Acylation and elimination of the NHC catalyst led to a β -lactone, which then underwent a [2+2] cyclo-reversion to form CO_2 and the observed cyclopentene **74**. They also reported a related reaction involving enals and unsaturated *N*-sulfonyl ketimines to form cyclopentane-fused β -lactams.^[28b]

2.1.3. Miscellaneous Cope Rearrangements—In an elegant total synthesis of strychnine, Kuehne and coworkers developed a complex Pictet-Spengler/Cope rearrangement trio to generate key tetracyclic intermediate **81** (Scheme 17).^[29] Studies using *p*-anisaldehyde, with which Cope rearrangement is not possible, indicate that although spiroindolene **78** can and likely does form as a mixture of four diastereomers, only one

adopts a conformation favorable for Cope rearrangement. Thus, prolonged heating funnelled the reaction through a single reactive diastereomer. Use of tryptophan-derived **75** resulted in formation of tetracycle **81** as a single enantiomer. This is a fine example of internal asymmetric induction.^[6b]

Tunge et al. reported a palladium-catalyzed decarboxylative C(sp³)—C(sp³) coupling reaction followed by palladium-catalyzed Cope rearrangement (Scheme 18).^[30] To effect decarboxylative coupling, β -ketoesters or alkylidene malononitriles, such as **83**, were treated with catalytic [Pd(PPh₃)₄]. In all cases examined, the predominant products were the allylated products (e.g. **84**) rather than the conjugated allylated products (e.g. **85**), indicating kinetic control in the reaction. When the conditions were altered to include higher temperatures, a decarboxylative coupling/Cope rearrangement duet was observed that allowed access to the thermodynamic γ -allylation products. In the presence of the Trost ligand **82**, high diastereoselectivity and moderate enantioselectivity were enforced.

In an uncommon example of Brønsted acid catalysis in a tandem Cope sequence, Dauben and Chollet observed an enol hydrolysis/Cope rearrangement duet (Scheme 19).^[31]

Seeking enone **87**, they were surprised to isolate instead enone **88**. The facile nature of the rearrangement suggested that acid catalysis was operational. Comparative studies on related 2-acyl-1,5-dienes gave credence to that proposal, as Cope rearrangement in the absence of acid occurred only upon heating.

In another unexpected Cope sequence, Krohn and Bernhard sought to synthesize α -hydroxy ketones en route to angucycline antibiotics (Scheme 20).^[32] Instead, treatment of allyl naphthols, such as **89**, with catalytic [Zr(acac)₄] and excess *t*BuOOH led to the isolation of *o*-quinones such as **92**. Initial hydroxylation was followed by oxy-Cope rearrangement and subsequent oxidation. Substrates with simple alkyl substituents that cannot rearrange resulted in the desired α -hydroxy ketones.

2.2. Claisen Rearrangement

The Claisen rearrangement, a heteroatom variant of the Cope rearrangement, was first discovered by Ludwig Claisen in 1912 (Scheme 21).^[33] The heteroatom of the Claisen rearrangement provides a much broader array of reactions

that can be combined into a tandem sequence. It also presents a functional-group handle that makes catalytic and asymmetric variants more feasible. Although the Claisen rearrangement is not strictly irreversible, reaction equilibria tend toward carbonyl-type products, thus also increasing its practicality in synthesis. A number of excellent reviews on the Claisen rearrangement have appeared.^[34] Catalytic tandem processes involving Claisen rearrangement can be organized loosely into the following types: tandem pericyclic processes, coupling and isomerization, and cyclization reactions.

2.2.1. Tandem Pericyclic Processes—The most conceptually simple tandem Claisen rearrangement is a duet involving two sequential [3,3] rearrangements. A powerful example of this on an industrial scale is exemplified by the BASF Citral process, in which acetal **96**

reacts with an acid catalyst to generate diene **97** (Scheme 22).^[35] Subsequent Claisen and Cope rearrangement efficiently give the important fragrant molecule **99**.

A europium(III)-catalyzed tandem Claisen/Cope rearrangement was reported by Metz and co-workers (Scheme 23).^[36] In their synthesis of the flavanoid 8-prenylnaringenin (**103**), they found that the europium-catalyzed tandem sequence presented a much more efficient route to preparing material needed for biological testing than the corresponding thermal process. Additionally, the Claisen/ Cope rearrangement duet was a more selective alternative to previous preparative methods, which suffered from low yields and/or relied on C prenylation. They found that **103** as well as the de-acetylated version of **101** both displayed strong estrogenic activities. Related thermal aromatic Claisen/ Diels–Alder cascades have been used by Nicolaou and Theodorakis to prepare complex polycyclic scaffolds in the syntheses of *Garcinia* natural products.^[37]

Tandem Claisen rearrangements have found great utility in the preparation of butenylidene-bridged aromatic compounds such as **107** for further use in the synthesis of rotaxanes, helicates, and other compounds that are structurally relevant to supramolecular chemistry (Scheme 24). Most commonly, the tandem rearrangement is performed under thermal conditions; however, Hiratani and co-workers reported a Lewis acid catalyzed variant that proceeded under milder conditions.^[38] Thus, treatment of allyl phenyl ether **104** with EtAlCl₂ at room temperature in the presence of 2-methyl-2-butene resulted in iterative tandem Claisen rearrangements. Intermediates **105** and **106** are depicted to highlight the process, even though the two sequences operate independently of each other.

In their formal synthesis of (–)-morphine, Chida and co-workers used iterative Claisen rearrangements to set the stereochemistry of the vicinal tertiary and quaternary carbon atoms of morphine in a single transformation (Scheme 25).^[39] Their strategy utilized the chiral pool by synthesizing enantiomerically pure trans-diol **109** from D-glucal. Treatment with catalytic 2-nitrophenol and ethyl orthoacetate at 140°C results in sequential Claisen rearrangements with good chirality transfer in moderate yield.

In some cases, cyclic enol ethers, presumed to arise from inverse hetero-Diels–Alder (IHDA) cycloadditions, have been shown to arise from a Diels–Alder/retro-Claisen rearrangement duet (Scheme 26). In their studies of unsaturated phosphonate reactivity, Hanessian and Compain observed Lewis acid sensitive ratios of the classic Diels–Alder adducts (analogous to **116**) and the IHDA product **114**.^[40] In work reported by Davies and co-workers,^[41] treatment of unsaturated aldehydes such as **115** resulted in isolation of a minor amount of Diels–Alder cycloaddition product **116** and a significant amount of the tandem DA/Claisen rearrangement product **117**. They determined, however, that direct IHDA competes under certain conditions. In both cases, isolation of the initial adduct and treatment under Lewis acidic conditions were used to support the tandem mechanism.

In their efforts to rapidly and efficiently access skeletons of iboga-type alkaloids, Neier and co-workers developed a Lewis acid catalyzed tandem Diels–Alder reaction involving thiocyanic acid ester **118** (Scheme 27).^[42] Following a methanol/triethylamine quench,

isothiocyanate **121** was isolated, which results from a [3,3]-sigmatropic rearrangement of the cyclohexadiene adduct.

The first report of a tandem Johnson–Claisen rearrangement/Diels–Alder reaction was by Mulzer and co-workers (Scheme 28).^[43] The distribution of products was sensitive to olefin substitution and the ring size of the product. The most selective transformation was that of allylic alcohol **122**, which upon treatment with ethyl orthoacetate and catalytic propionic acid underwent a reaction trio.

Indeed, methods combining the Claisen rearrangement in tandem with one or more other pericyclic reactions are very powerful, as they are often stereoselective at each stage. Drawing on reports that enantiomerically pure copper(II) bis(oxazolines) asymmetrically catalyze Claisen rearrangements and intermolecular carbonyl-ene reactions independently, Hiersemann and co-workers successfully applied these catalysts in a tandem process (Scheme 29).^[44] Treatment of allyl vinyl ether **126** with catalytic [Cu{(S,S)-Ph-Box}] (OTf)₂ resulted in isolation of cyclohexanol **128** in high yield, good diastereoselectivity, and outstanding enantioselectivity. Based on their previous work on the catalyzed Claisen rearrangement, they were able to conclude that the ene reaction proceeds with almost complete enantioselectivity and that the low diastereoselectivity observed is a result of incomplete enantioselectivity on the part of the Claisen rearrangement. The selectivity in the ene reaction is thus completely catalyst controlled.

2.2.2. Metal-Catalyzed Coupling/Claisen Rearrangement and Isomerization/Claisen Rearrangement—Exploration of various strategies to synthesize vinyl ethers have revealed many challenges, thus their preparation as intermediates in tandem processes presents a great improvement. The Johnson–Claisen rearrangement (see above Scheme 25 and 28) is itself a tandem reaction; it involves initial acid-catalyzed condensation of orthoformates with allyl alcohols to form reactive ketene acetals.^[45] Metal-catalyzed couplings or isomerization reactions are attractive strategies to generate vinyl ethers in situ, and the following examples represent advances in this area.

Buchwald and Nordmann reported a copper-catalyzed coupling reaction of allylic alcohols and vinyl iodides to generate Claisen substrates (Scheme 30a).^[46] For example, 2-hexen-1-ol and vinyl iodide **129** reacted in the presence of CuI to generate diene **131**, which underwent further rearrangement to aldehyde **132**. The observed relative stereochemistry was consistent with a chair-like transition state for the Claisen rearrangement. Palladium-catalyzed coupling of allylic alcohols with triethylene glycol divinyl ether, as reported by Wei and co-workers, also gave allylic vinyl ether substrates for Claisen rearrangement (Scheme 30b).^[47] Their method could be performed on a kilogram scale. Copper and palladium catalysts provide good alternatives to the use of toxic mercury(II) catalysts commonly used for the preparation of vinyl enol ethers.

Wood and co-workers disclosed a rhodium-catalyzed carbene insertion coupling methodology in tandem with a Claisen rearrangement (Scheme 31).^[48a] In these duets, allylic alcohols inserted into rhodium carbenoids with proton transfer to generate allyloxy enols (many of which could be observed by ¹H NMR spectroscopy), such as **137**.

Mechanistic studies highlighted the inherent propensity of allyloxy enols to undergo Claisen rearrangement. The facile nature of the rearrangement is what allowed the tandem sequence to proceed beyond the formation of simple O–H insertion products. When enantiomerically enriched allylic alcohols were used, a number of α -hydroxyketones could be isolated in good yield with transfer of chirality. The methodology was used in the total synthesis of (+)-latifolic acid^[48b] as well as the synthesis of the welwitindolinone skeleton.^[48c]

During their studies on welwitindolinone, attempts to isolate the key α -hydroxyketone **141** were accompanied by aketol rearrangement to **142** (Scheme 32).^[48c] In the total synthesis of furanosylated indolocarbazoles (+)- and (–)-K252a, the hydroxyketones were deliberately treated with $\text{BF}_3 \cdot \text{OEt}_2$ to effect the rearrangements (not shown), thus efficiently promoting such a Claisen rearrangement trio.^[48d]

In a related carbene trapping reaction, one that could also be called a “metallo-Claisen” rearrangement, Trost and coworkers utilized the propensity of alkynes to isomerize to metal vinylidene complexes and generate carbenoid intermediates by trapping with allyl alcohols (143 to 145, Scheme 33).^[49] [3,3] Rearrangement to a ruthenium–acyl complex and reductive elimination terminated the reaction trio to generate a g,d-unsaturated ketone 148. An allyl isomerization was invoked to account for the observed selectivity.

Two authors of this review used rhodium carbenoids to effect an isomerization reaction that allowed alternative in situ preparation of vinyl enol ethers (Scheme 34).^[50] This method addressed the difficulty associated with stereoselectively preparing *Z*-enol ethers. Additionally, their transformation, which relied on the in situ generation of a diazo compound, expanded the arena of utility to non-carbonyl-stabilized carbene precursors. Thus, *N*-aziridinyl imines, such as **149** (i.e. Eschenmoser hydrazones), thermally decomposed by chelotropic extrusion in the presence of rhodium(II) catalysts to produce rhodium–carbenoid intermediates, which isomerize controllably to form *Z*-enol ethers. In the specific case of enol ether **150**, subsequent addition of Me_2AlCl led to aldehyde **151** by a Claisen rearrangement trio. If DIBAL was used, a reductive rearrangement generated alcohol **152**.

Conversely, the presence of an additional double bond resulted in tandem ene or Cope reactions (Scheme 35). Treatment of neryl ether 153 with rhodium acetate followed by a Lewis acid induced cascade terminated in a carbonyl-ene reaction to produce cyclohexenol **155** with excellent diastereoselectivity, while α,β -unsaturated hydrazone **156** underwent a Bamford–Stevens/Claisen/Cope rearrangement cascade to produce aldehyde **158**. Both sequences proceed by relatively rare quartet ensembles.

Metal-catalyzed isomerization of bis(allyl) ethers has also been a fruitful strategy for the in situ generation of Claisen substrates. The strategy was originally reported by Reuter and Salomon using ruthenium catalysis.^[51] During explorations in the realm of ruthenium-catalyzed alkene metathesis, Dixneuf and co-workers discovered an alternate reactivity pattern involving tandem isomerization/Claisen rearrangement (Scheme 36).^[52] They used a three-component catalyst system (ruthenium, NHC, base) to catalyze the isomerization of 1,6-diene **159** to an intermediate vinyl ether, which underwent Claisen rearrangement to g,d-

unsaturated aldehyde **160** in good yield. Double isomerization of 1,7-diene (allyl homoallyl) systems could also be accomplished.

Schmidt explored the competition between isomerization/ Claisen rearrangement and alkene metathesis (Scheme 37). The ability to control the pathway by judicious choice of reaction conditions in any given substrate system increases the diversity of products that can be generated using a single catalyst.^[53] Whereas Grubbs I catalyst, $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}]$, rapidly catalyzed conversion of diene **162** to the dihydrofuran **163**, it was reasoned that the isomerization reactivity of the ruthenium carbene could be enhanced by formation of a ruthenium-hydride species. Schmidt and coworkers exploited Grubbs observation that $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHOEt}]$ (formed by the reaction of $[\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}]$ with electron-rich olefins) decomposes to the ruthenium-hydride complex $[\text{RuHCl}(\text{CO})(\text{PCy}_3)_2]$ upon heating. Thus, by altering the alkene metathesis conditions to include ethyl vinyl ether, they were able to switch the reactivity almost entirely to the isomerization/Claisen pathway to preferentially generate aldehyde **164**.

Iridium catalysts are also effective for the isomerization duet.^[54,55] In their work on quinone monoketals, Swenton and co-workers observed that quinol vinyl ethers **165** could be converted thermally and photochemically to spiro-fused 2,5-cyclohexadienones **166** through [1,3] rearrangement (Scheme 38). Although [3,3] rearrangement is not feasible in such substrates, they were interested in understanding the competition in substrates where [1,3] and [3,3] rearrangements were both sterically and electronically possible. As a result, they reported an iridium-catalyzed isomerization/ Claisen rearrangement/cyclization trio (**167** → **170**).

Nelson^[56] and co-workers reported a strategy that combined the addition of dialkyl zinc reagents to aldehydes catalyzed by asymmetric aminoalcohols with the iridium-catalyzed isomerization/Claisen rearrangement (Scheme 39). Of paramount importance was finding a catalyst to achieve selective isomerization without epimerizing the aldehyde product. Thus, consecutive nucleophilic addition and palladium-catalyzed etherification of cinnamaldehyde with diethyl zinc and allyl acetate generates bis(allyl) ether **172** in high yield and enantioselectivity. Iridium-catalyzed isomerization of the terminal allyl group followed by rearrangement afforded aldehyde **173** with negligible loss of enantioselectivity. The duet could be expanded to a reduction trio by quenching with NaBH_4 .

This method was also applied to 1,6-enynes in a report by Tanaka and co-workers (Scheme 40).^[57] When enyne **174** was treated with a rhodium(I) catalyst, allenic aldehyde **175** was generated. At high temperatures, the allenes isomerized further to generate dienals such as **176**. The mechanism of this carbonyl migration was proposed to proceed by initial insertion in the aldehyde C–H bond.

Eilbracht and co-workers developed a rhodium(I)-catalyzed tandem Claisen rearrangement/hydroacylation reaction duet of allyl vinyl ethers to form cyclopentanones.^[58] They then expanded the reaction to include an isomerization to generate the allyl vinyl ethers in situ (Scheme 41). In the rearrangement trio, bis(allyl) ethers such as **178** were treated with a rhodium(I) or ruthenium(II) catalyst. Isomerization to vinyl enol ethers such as **179** was

followed by Claisen rearrangement to aldehyde **180**. The quaternary center at C3 was necessary to block double bond isomerization to generate α,β -unsaturated aldehydes, a common side reaction under these conditions. Intramolecular olefin hydroacylation then proceeded to generate cyclopentanone **181**. They have demonstrated the utility of the Claisen/hydroacylation in the preparation of spirocyclic precursors to sesquiterpene natural products, and a polystyrene-supported catalyst has also been shown to be effective for the duet.

Ovaska and co-workers made extensive use of an anionic cyclization/Claisen rearrangement duet in the rapid synthesis of relatively complex polycyclic structures (Scheme 42).^[59] For example, in the formal total synthesis of frondosin A, treatment of allylic alcohol **182** with a substoichiometric amount of methyllithium proceeded to cycloheptene **184** as a mixture of diastereomers. Epimerization in basic methanol increased the ratio to favor the desired isomer. The versatility of the method was shown by the ability to use structurally isomeric **185** to generate **186**, also a viable precursor to frondosin A. A gold-catalyzed cationic variant of this reaction is presented in Section 2.2.5, Scheme 63.

A related rearrangement that involves p -alkyne activation is the platinum-catalyzed carboalkoxylation/Claisen rearrangement duet (Scheme 43).^[60] Yamamoto and co-workers reported the platinum(II)-catalyzed cycloisomerization of saturated cyclic acetals to 1,2-dialkoxyindenes, related to structure **188**. When the acetal contained a double bond, as in **187**, the carboalkoxylation was followed by Claisen rearrangement to give bridged bicycle **189**.

In an elegant demonstration of the importance of understanding catalyst structure and reactivity when designing a new tandem reaction, Chatani and co-workers reported a rhodium(I)-catalyzed [2+2+1] carbonylative cycloaddition/Claisen rearrangement duet of phenoxide-substituted diynes **190** (Scheme 44).^[61] To that point, the carbonylative cycloaddition of diynes had rarely been studied, and the strong binding of product cyclopentadienes to the rhodium catalyst was recognized early as a barrier to developing a catalytic process. Having isolated and characterized cyclopentadiene-bound rhodium complex **193** by X-ray crystallography, they considered ways to release the catalyst for turnover. Introduction of an aryl ether substituent resulted in [3,3]-sigma-tropic rearrangement to **192**, a more weakly coordinating product. In fact, the rearrangement benefits from coordination by rhodium; this aromatic Claisen rearrangement proceeds at 120°C while much higher temperatures (> 200°C) are typically required. Thus, treatment of diyne **190** with catalytic rhodium(I) under CO atmosphere and with heating produced phenol **192** in moderate yield.

2.2.3. Claisen Rearrangement/Cyclization—A variety of N and O heterocycles can be synthesized using tandem Claisen reactions. For example, aromatic ether **194** in the presence of catalytic AlCl₃ at -70°C rearranges to cyclic ether **195**, presumably via a phenol intermediate (Scheme 45a).^[62a] Similar transformations were catalyzed by gold, iridium, molybdenum, zinc, titanium, and zeolites.^[62b–h] The sequence could be taken one step further, as in the copper-catalyzed rearrangement trio reported by Adio and co-workers (Scheme 45b).^[63a] The transformation proceeded by initial hydroalkoxylation to form allyl

aryl ethers (e.g. **198**), which then underwent a Claisen rearrangement to allyl aryl compounds (e.g. **199**). In contrast to the preceding duets, a 6-endo-trig cyclization terminates the sequence. Annulation strategies such as these have been reported previously using other Brønsted and Lewis acid catalysts. However, a caveat should be mentioned: an intermediate Claisen rearrangement has not always been suggested to explain the formation of the aryl–bond, nor has it been confirmed in the aforementioned case.^[63b–f]

Binder and Kirsch combined Claisen rearrangement with in situ amine condensation for use in the synthesis of pyrroles (Scheme 46). Their rearrangement trio commenced with a silver-catalyzed Claisen rearrangement. An aryl amine and a gold catalyst were subsequently added to the presumed allenyl ketone intermediates. Condensation and cyclization thus provided methylpyrroles such as **203**. Although gold catalysts should be able to effect the initial Claisen rearrangement, yields were unfortunately lower when all reagents were initially present.^[64] Gold-catalyzed rearrangements of prop-argyl enol ethers have also been reported by Toste.^[65]

Methylpyrroles could also be obtained from propargylenamines through a related amino-Claisen/cyclization duet reported by Saito and co-workers (Scheme 47).^[66] The same

authors developed a rhodium-catalyzed amino-Claisen cyclization duet to generate indoles. The reaction could be combined with in situ synthesis of propargyl amines, extending the sequence to a trio.^[67] For example, treatment of a pre-mixed solution of bromobutynone and aniline with rhodium catalyst in the presence of base and phosphine at reflux in hexafluoroisopropyl alcohol (HFIP) produced indole **208** in good yield.

In a report by Liu and co-workers,^[68] gold(III) and silver(I) salts were combined to catalyze the Claisen rearrangement of (aryloxymethyl)alkenoates. Subsequent lactonization terminated the duet (Scheme 48). Thus, treatment of naphthyl ether **209** with AuCl₃ and AgOTf in DCE or DCB at 120°C led to isolation of dihydrocoumarin **211** in good yield. At low temperatures and in cases where substituents disfavored the [3,3] rearrangement, a competing [1,3] rearrangement proceeded via an allyl cation/phenoxide ion pair to generate isomeric dihydrocoumarins.

Propargyl esters are increasingly studied substrates in the context of enyne cycloisomerization reactions because of their propensity to undergo gold- or platinum-catalyzed 1,2-and/or 1,3-acyl migration reactions.^[69] Rhodium catalysts have also been shown to be effective for the process.^[70] The 1,3-acyl migration is a formal [3,3]-sigmatropic rearrangement that generates allenyl acetates, which under catalyzed conditions are themselves activated by the metal to undergo further rearrangements (Scheme 49). Toste and co-workers showed that the process was reversible, so tandem chemistry is again required to complete the reaction and achieve selectivity.^[71] The allenyl acetate formed could be captured in many ways, such as by a pendant nucleophile (Scheme 49a)^[72] or Nazarov cyclization (Scheme 49b).^[73a] In one case, trapping with a pendant indole resulted in a formal [2+2] reaction duet (Scheme 49c).^[73b] The intermediate allenyl acetates could also undergo further isomerization reactions^[74] or trapping with an external nucleophile.^[75] Only a few of the multitude of possible reactions are shown here; for further information we

direct the reader to reviews by Tang,^[70] Zhang,^[76] and Marion.^[69] The propargyl esters could also participate in a 1,2-acyl shift leading to metal intermediates that display carbene-like reactivity;^[77] for combination with a [2,3] rearrangement, see Section 3.1 (Scheme 87 and 88).

Gevorgyan and co-workers reported a copper-catalyzed [3,3] rearrangement/cycloisomerization duet involving phosphatyloxy alkynyl ketones such as **218** (Scheme 50).^[78] This reaction involved the rearrangement of a phosphate ester (see analogous propargyl ester Claisen; Scheme 49) and was followed by cyclization to form furans. Bicyclic products could also be obtained when alkynyl pyridines such as **221** were used. Oxygen isotope labelling provided support for the [3,3] rearrangement pathway; interestingly, under these conditions the standard carboxylic ester substrates did not appear to undergo the Claisen-type rearrangement, but instead formed similar products by alternate rearrangement mechanisms.

2.2.4. Claisen Rearrangement/Coupling—The following reactions are unified in that they combine Claisen reaction with a C–C bond-forming event. During studies of 2-allyloxy pyridines as substrates in the chelation-controlled Heck reaction, Itami and co-workers discovered a Claisen rearrangement/Heck reaction duet (Scheme 51).^[79] Treatment of allyloxy pyridines such as **223** with palladium, followed by addition of aryl iodides and base, resulted in formation of N-substituted 2-pyridones in good yield and selectivity for *E* olefins.

As part of their substance **P** antagonist programme, Watson and co-workers sought a route to spiroindane **229** (Scheme 52).^[80] Since α -allyl ketone **228** could not be synthesized by direct C alkylation, they instead explored a palladium-catalyzed Claisen rearrangement. When allyl enol ether **226** was heated in the presence of [Pd(PPh₃)₄], the rearrangement terminated at amide **228**. When the reaction was performed in the presence of base, subsequent intra-molecular Heck reaction allowed access to amide **229**. Use of a crotyl analogue of **226** indicated that the reaction proceeds via a π -allyl/enolate ion pair, rather than a palladium(II)-accelerated cyclic sigmatropic transition state.

Wipf and co-workers developed an asymmetric zirconocene-mediated Claisen rearrangement/carboalumination duet.^[81b] They have since expanded on that tandem sequence by developing a zirconocene-catalyzed carboalumination of alkynes in the presence of enol ethers.^[81a] The resultant trio led to the isolation of 1,6-dienes (Scheme 53). Zirconium-catalyzed carboalumination of alkynes led initially to vinyl alanes such as **231**. The vinyl alane itself could then serve as a Lewis acid for the catalysis of Claisen rearrangement of vinyl enol ether **232**. Vinyl transfer from the alane to the resultant aldehyde **233** generated allylic alcohol **234** with good selectivity. Water is a key accelerating additive for these sequences.

The Claisen rearrangement has also been coupled with alkene metathesis. Specifically, Sutherland and co-workers combined the asymmetric Overman rearrangement, a hetero-Claisen variant involving trichloroacetimidate **237**, with a ring-closing metathesis to synthesize the cyclic allylic trichloroacetamide **239** (Scheme 54).^[82,104] The Overman

rearrangement has wide appeal since the trichloroacetamide handle has utility for a number of subsequent transformations, and use of the enantiopure palladium complex (S)-COP-Cl makes it catalytic and asymmetric.^[83] Trichloroacetamide 239 was used in a synthesis of the tropane alkaloid (+)-physoperuvine.^[82a]

Borrelly and Paquette used a Claisen rearrangement/ Sakurai cyclization duet to prepare vinyl bromide 245, a cyclopentenyllithium reagent precursor that is important in their efforts toward the total synthesis of natural products (Scheme 55).^[84] Treatment of vinyl enol ether **242** with Et₂AlCl, followed by HCl and TBAF in the workup, resulted in facile formation at room temperature of the vinyl bromide **245**, presumably via intermediate aldehyde **243**. Thermal conditions were unsuccessful.

Another set of atypical Claisen rearrangements are the transpositions invoked in oxidative processes mediated by classic chromium reagents, that is, metallo-Claisen rearrangements (see also Scheme 33).^[85] A catalytic tandem variant of this process was developed by Trost and co-workers using vanadium (Scheme 56).^[86] The transposition of allenic alcohols had previously been unexplored and it was anticipated that the products would be reactive enolates. Thus, treatment of allenic alcohols such as **246** with an oxo-vanadium catalyst resulted in rearrangement to enolate **248**. Subsequent capture by benzaldehyde terminated the aldol reaction duet.

In an impressive combination of four elementary events, Miller and co-workers reported Claisen rearrangement quartets initiated by palladium-catalyzed alkyne coupling.^[87] Treatment of aryl or aroyl halides ("R-X") with alkynes in the presence of palladium(II) generated aryl or aroyl alkynes, such as **252** (Scheme 57). Isomerization of the resultant propargyl ether led to allenyl ethers that could undergo subsequent Claisen rearrangement to a key diene intermediate **254**. Intermediate **254** underwent an array of subsequent pericyclic reactions, depending on the electronic nature of the substituents (Scheme 58).

2.2.5. Charge-Accelerated Claisen Rearrangement—Allylic ethers, amines, and sulfides can add to ketenes to generate zwitterionic intermediates (e.g. **263**, Scheme 59), which undergo facile [3,3] rearrangement, a variant known as the Belluš–Claisen rearrangement.^[88] Such duets have been used extensively for the formation of building blocks for natural product heterocycle synthesis, and benefit from exceptional asymmetric induction when enantiopure substrates are used.^[89] Although stoichiometric amounts of Lewis acids are typically required, MacMillan and co-workers^[90] made a significant advance in showing that asymmetric induction could be externally controlled by the Lewis acid.^[90a] The reaction could be extended a step further when allyl diamines were used (Scheme 59).^[90c] The initial [3,3]rearrangement was proposed to proceed through the (E)-ammonium intermediate **261**, wherein pseudo 1,3-diaxial interactions are minimized. Minimization of (1,2) allylic strain was then proposed as the driving force for the subsequent [3,3] rearrangement of ammonium **263** to selectively generate the 2,3-syn-3,6-anti isomer **264**. The preparation of said 1,7-diamidoheptane represents a rapid method for preparing a stereochemical motif commonly found in macro-lide antibiotics. The ability to selectively cleave the α,β disubstituted amide using an iodolactonization/ring-opening sequence demonstrates further the utility of this process.

A number of related charge-accelerated Claisen rearrangements have been reported. For example, Brønsted or Lewis acid catalyzed amine addition to alkynes^[91] or allenes^[90b] results in vinyl ammonium intermediates poised for [3,3] rearrangement (Scheme 60a,b). A base-catalyzed isomerization/rearrangement trio of propargylammonium salt **273** was reported by Honda and co-workers (Scheme 60c).^[92] Previously, ammonium salts under basic conditions generated ylides that underwent [2,3] rearrangement. With protic solvents, base deprotonation (catalytic in principle) led to alkyne–allene isomerization, which was then followed by [3,3] rearrangement and in situ reduction.

In synthetic efforts toward analogues of naturally occurring prostaglandins, Florent and co-workers developed a related ionic aza-Claisen/Mannich trio (Scheme 61).^[93] Treatment of either diastereomer of aldehyde **277** with pyrrolidine resulted in a crude mixture of enamine isomers **278**. Alkylation with an allylic iodide generated the ammonium **279**, which underwent facile [3,3] rearrangement to iminium **280**. They expected to isolate the aldehyde derived from **280**, but were pleased to isolate instead cyclopentenone **282**. Thus, an immediate Mannich cyclization occurred through nucleophilic attack of the pendant MOM-protected enol ether. Finally, pyrrolidine β-elimination terminated the alkylation/Claisen/Mannich quartet. The poor overall diastereo-selectivity is likely linked to the mixed enamine stereochemistry of **278**.

Rainier and co-workers reported a related tandem reaction that involved formation of a 1,3-dipole from a thioether and a rhodium carbenoid (Scheme 62).^[94] In their case, thioether addition to the carbene led to the formation of the intermediate sulfur ylide, **285**. They proposed that proton transfer precedes the [3,3]-sigmatropic rearrangement to give indoline **286**. The reaction displayed high diastereoselectivity for certain substrates. The methodology provided an attractive route to substituted indolines with a quaternary carbon center and could also be used to prepare indolines with vicinal quaternary carbon centers. The products formed have significant potential for use in the total synthesis of bioactive indoline natural products.

While Ovaska's alkoxide cyclization conditions may be considered relatively harsh (see above, Scheme 42), the Lewis acid catalyzed Claisen rearrangement of cyclic enol ethers to form cycloheptenones provides an alternate method that fits within the context of charge-accelerated Claisen rearrangements. Although the strong Lewis acids used therein demand the consideration of functional-group compatibility,^[95] Rhee and co-workers reported an extremely facile sequence that formally corresponds to the same type of duet as in Ovaska's work (Scheme 63).^[96] Treatment of 3-alkoxy-1,6-enynes with a gold(I) catalyst (and AgSbF₆ to favor the formation of cationic gold) resulted in rapid isomerization initially to the isolable methyl enol ether **290**. The transfer of stereochemical information from the trans double bond of **288** strongly supported the concerted nature of the rearrangement.

2.3. Cationic Hetero-Cope Rearrangements

The “aza-Cope rearrangement” most commonly refers to the “2-aza-Cope rearrangement” of iminium ions (**293** → **294**, Scheme 64). While the “oxy-Cope rearrangement” generally refers to rearranging p systems with appending oxygen substituents, the “oxonia-Cope rearrangement” is the term given to the oxocarbenium analogue of the aza-Cope

rearrangement of iminium ions. This section will focus on the incorporation of the cationic aza-Cope and cationic oxonia-Cope rearrangement within catalytic tandem sequences.

2.3.1. Aza-Cope Rearrangements—In many instances, the aza-Cope rearrangement is itself a reaction duet, initiated by acid-catalyzed condensation between an amine and carbonyl group to form a reactive iminium ion. The aza-Cope rearrangement was first invoked to explain a C–C cleavage reaction in the reductive alkylation of homoallylic amine **295** (Scheme 65).^[97] In this case,

condensation between formaldehyde and the benzylamine generates iminium **293**, which rearranges to iminium **294**. Hydrolysis leads to formation of homoallylic amine **296**, and it is this amine rather than the starting material **295** that is alkylated through reductive amination to the tertiary amine **298**. Formic acid is the reductant.

Recently, Rueping and Antonchick reported a catalytic enantioselective variant that utilized the enantiopure binol phosphoric acid derivative **303** (Scheme 66).^[98] Enantioselectivity was proposed to arise from a strong ion-pair interaction (E) between the protonated imine and the anionic phosphate. This method expands the available routes for preparing optically active homoallylic amines, which are important building blocks in natural product synthesis.

As with the parent Cope and Claisen rearrangements, the aza-Cope rearrangement displays good stereocontrol through a chair-like transition state. Use of a judiciously placed substituent led to the observation by Overman and coworkers of a dynamic kinetic resolution in the aza-Cope rearrangement (Scheme 67).^[99] The possibility of resolution was deduced from the observation that iminium ions such as **305** can epimerize rapidly by a fast equilibrium with enammonium ions **306**. Thus, treatment of amine **304** with trifluoroacetic acid, dimedone, and morpholine, followed by quenching with benzyl chloroformate, leads to isolation of carbamate **308** as a single diastereomer in high enantiomeric excess. The full transformation constitutes an iminium ion aza-Cope/acylation quartet if you include initial acetal hydrolysis. The dynamic kinetic resolution occurs, because aza-Cope rearrangement proceeds slowly, but selectively, via diastereomer **305a**. Trapping of the thermodynamically less stable iminium **307** by dimedone is fast, so that the aza-Cope rearrangement is rendered effectively irreversible. Rearrangement of **305a** across the concave face by a chair-like transition state is more facile, as it places the phenyl substituent in a pseudo-equatorial orientation, whereas in **305b** that substituent would be placed in a pseudo-axial position.

Tehrani and co-workers combined the Lewis acid catalyzed aza-Cope rearrangement with a Petasis reaction (Scheme 68).^[100] Addition of an alkynylborate salt generated not the product of direct addition (**311**), but instead the rearranged amine **314**. BF₃ coordination catalyzes the aza-Cope rearrangement to isomeric iminium **313**. Acetylide addition to this more reactive iminium compound leads to amine **314** upon workup. The Petasis reaction shares some mechanistic steps with the Mannich reaction, and tandem aza-Cope/Mannich reactions have long been known to have excellent utility in the preparation of nitrogen-containing heterocycles. They are discussed further below.

In their research aimed at the design of methods to prepare α -amino acids, Agami and co-workers made use of glyoxyl condensation/aza-Cope rearrangement trios (Scheme 69).^[101] Two possible pathways could be observed, depending on the nucleophile present (water or formic acid) to trap the reactive iminium ion. The reactions were initiated by spontaneous condensation between glyoxal- and phenylglycinol-derived amino alcohol **315** to generate iminium **316**. Aza-Cope rearrangement generated iminium ion **317**. In the presence of water, the iminium compound was cleaved to form amine **318** in good yield through an uncatalyzed condensation/aza-Cope/hydrolysis trio. On the other hand, in the presence of the weaker formic acid nucleophile, iminium ion **317** underwent a further iminium-ene cyclization, the product of which was trapped to form bicycle **319**, thus concluding a condensation/aza-Cope/iminium-ene cyclization quartet. Waters and co-workers combined a similar condensation/aza-Cope reaction with silver-mediated [3+2] cyclo-addition in a consecutive reaction trio.^[102]

The aza-Cope/Mannich sequence represents by far the most developed tandem sequence involving an aza-Cope rearrangement (Scheme 70). It was developed by Overman in the late 1970s and was specifically designed to capitalize on both the acceleration of rearrangements involving charged species and the tandem intramolecular trapping of a reactive iminium ion to render the aza-Cope rearrangement effectively irreversible.^[103] When the iminium ion is formed by an intramolecular reaction involving a pendant carbonyl group, complex polycyclic structures result. The method has been used to great success to construct complex natural products, including Overman's own elegant synthesis of actinophyllic acid.^[103c] For a personal account of Overman's methods development in the broad area of Claisen rearrangements, see reference [104].

Brummond and co-workers used the condensation/aza-Cope/Mannich reaction trio in the formal synthesis of a tricyclic immunosuppressant.^[105] Condensation of amino ketone **323** to form iminium **324** demonstrated the feasibility of proceeding through a bridgehead iminium ion (Scheme 71). Rearrangement and enol ether attack on iminium **325** led to the isolation of tricycle **326** as a mixture of diastereomers. Because of the instability of the aldehyde, it was protected as a ketal (72% yield after two steps). A more functionalized substrate was also competent in the reaction and used for the preparation of an advanced intermediate toward immunosuppressant FR901483.

The aza-Cope/Mannich sequence has been utilized to great extent in synthesis and medicinal chemistry,^[106] and solid-supported acid resins^[107] have been developed to effect the transformation.

2.3.2. Oxonia-Cope Rearrangement—The oxygen analogue of the cationic aza-Cope rearrangement is typically referred to as the oxonia-Cope rearrangement (not to be confused with oxy-Cope rearrangements, see Section 2.1.2). The term oxa-Cope rearrangement is sometimes used, but this term has also been applied to the Claisen rearrangement. Historically, the oxonia-Cope rearrangement has been considered mainly as a competing background process in the ene cyclization of oxocarbenium ions (i.e. the Prins reaction; Scheme 72). Overman and co-workers had originally designed this reaction after the success of the Cope rearrangement of iminium ions, but found that the oxocarbenium analogues

followed a different pathway. The isolated products instead implicated a Prins cyclization/pinacol rearrangement pathway.^[103a,104]

The mechanism of the oxonia-Cope rearrangement was first invoked by Speckamp and co-workers in their reports on the acid-mediated π cyclizations of α -methoxycarbonyl oxycarbenium ions to form oxacyclic carboxylic esters.^[108] Although such cyclization reactions fall outside the scope of this article, there is a significant body of work, particularly by Rychnovsky,^[109] that suggests the oxonia-Cope rearrangement is a background process for many of them.^[110] The background process can be detrimental to stereoselective processes, and can be minimized.^[111]

The oxonia-Cope rearrangement product can sometimes be selectively intercepted. The cationic intermediates can be captured by a pendant or external nucleophile, lose a proton to form alkene products, or be hydrolyzed to release homo-allylic alcohols. For example, the oxonia-Cope rearrangement without a competing Prins cyclization has been developed by Nokami and co-workers as an improved method for α -selective allylation of aldehydes (Scheme 73).^[112] While many allylic transition-metal reagents preferentially give γ adducts, such as homoallylic alcohol **331**, the α -selective allylation is synthetically more challenging. Rearrangement via oxocarbenium ions was seen as a way to isomerize undesired (but easily synthesized) γ adducts. The reaction is driven toward products that are derived from more stable cations or those that contain less hindered alcohols and more stable olefins. While the original reaction was planned with a stoichiometric amount of aldehyde, it was shown that a catalytic amount of aldehyde is sufficient to promote the isomerization. Stereo-chemical fidelity is observed when enantiomerically enriched alcohols are used, confirming the predictive stereocontrol provided by the cyclic transition state. Loh and co-workers showed that indium(III) was a competent oxonia Cope/cyclization catalyst and observed two different reaction quartets (Scheme 74).^[113] At the outset of their studies, they sought to expand Nokami's methodology, which was less effective with prenyl adducts. Loh proposed to thus explore the stronger Lewis acid In(OTf)₃ in the allyl-transfer exchange reaction. Instead of the expected homo-allylic alcohol **341**, they observed further reactivity depending upon the amount of excess aldehyde. With a catalytic amount of aldehyde, oxocarbenium **338** was hydrolyzed to generate the expected alcohol. Indium then catalyzed the cyclization to form tetrahydrofuran **335**. With a full equivalent of aldehyde, an oxonium-ene cyclization proceeded presumably to tertiary cation **339**. Oxygen [1,3] shift followed by proton transfer led to the formation of alkene **336**. The intermediacy of alcohol **341** was verified by separate control experiments. Despite the unexpected reactivity in this case, the method was later successfully expanded to the preparation of α -prenylated aldehydes by careful selection of the prenylated donor alcohol. The oxonia-Cope rearrangement continues to be used in the preparation of α adducts in methodology development^[114] and total synthesis.^[115] Transfer of chirality is generally very good in these reactions, and stereodefined products are often obtained.

Ramachandran and co-workers observed adduct isomerization following crotyl borane addition to aldehydes in tandem oxonia-Cope rearrangements (Scheme 75).^[116] For the case of vinyl esters such as **342**, the rearrangement was terminated by lactonization. Lewis acid accelerated crotylboration led initially to γ adduct **343**. In the presence of a ytterbium(III)

catalyst, lactonization without rearrangement to form lactone **348** occurred. Conversely, with an indium(III) catalyst, acetal formation and elimination resulted in the formation of oxonium ion **344**. Oxonia-Cope rearrangement to **345** was followed by regeneration of the borate ester adduct **346**. Lactonization then provided rearranged **347** in good yield.

In a Lewis acid mediated oxonia-Cope rearrangement trio Rychnovsky and co-workers utilized a Mukaiyama–Michael addition to generate a reactive oxocarbenium ion in situ (Scheme 76).^[117] Treatment of enol ethers such as **349** with TiBr₄ (catalytic in principle) and **350** resulted in a Michael addition to generate oxocarbenium **351**. [3,3] Rearrangement to oxocarbenium **352** followed by cyclization generated tetrahydropyran **353** in good yield. The appropriate placement of a tethered nucleophile favors oxonia-Cope rearrangement without a Prins cyclization “interrupting”. Rychnovsky used this strategy to great success in other, non-catalytic sequences.^[118]

3. [2,3]-Sigmatropic Rearrangements

Although [2,3]-sigmatropic rearrangements are far less ubiquitous in organic synthesis, they present many features similar to the more utilized [3,3] counterparts that make them attractive strategies. Virtually all known [2,3] rearrangements involve heteroatoms,^[119] commonly N, O, and S, and are generally divided into two types (Scheme 77). They often proceed with high stereoselectivity; the higher conformational flexibility of five-membered cyclic transition states suggests that they are more susceptible to the effects of stereochemical control by substituents. This has been summarized in detail by Hoffmann.^[120]

Type I reactions encompass anionic rearrangements such as the Wittig rearrangement.^[122] They typically involve the stoichiometric, irreversible generation of an anion, and so none are included in this review. Conversely, type II rearrangements encompass ylide reactions such as the carbon-oxonium ylide rearrangement. Because of the recent increase in the number of methods involving catalytic generation of ylides from diazo compounds,^[123] several examples are discussed in the current review.

3.1. Carbon Ylides

There have been a number of reports on the metal-catalyzed ylide formation/[2,3]-sigmatropic rearrangement duet using α -diazocarbonyl compounds and sulfides,^[124] ethers, and amines.^[125] These methods have provided a much milder alternative to stoichiometric base-promoted methodologies. Competing carbenoid reactions (e.g. carbene dimerization, C–H insertion, cyclopropanation, and Stevens [1,2] rearrangement), some of which are discussed in Section 4, and catalyst deactivation by the heteroatom have presented the main challenges to their development. Many asymmetric variants have been reported.^[126]

The intermolecular coupling of diazo compounds with sulfides through [2,3] rearrangement is known as the Doyle–Kirmse reaction, itself a sulfur ylide duet (Scheme 78). Initial developments by Doyle and co-workers^[127] provided homo-allyl sulfides (e.g. **356** or **359**) in good yields from the reaction of allyl sulfides and ethyl diazoacetate, but relied on a high excess of diazoester and the slow addition of sulfide. Although rhodium is most commonly

used to generate sulfonium ylides, Carter and Van Vranken showed that palladium was a suitable catalyst for the transformation and that iron was even better.^[128] Use of iron offered two key improvements to the methodology: the slow addition of reagents was unnecessary and the excess of diazo compound could be reduced significantly.

As the methodology evolved, asymmetric variants have been reported using enantiomerically pure phthalimido piperidinone dirhodium(II) catalysts^[129] as well as diastereoselective variants using enantiopure allylic sulfides.^[130] Intramolecular insertion/rearrangements via sulfonium ylides are also known.^[131]

Related reactions of diazo compounds and ethers via oxygen ylides have also been developed. Johnson with Roskamp and Pirrung with Werner independently reported the first intramolecular carbenoid insertion/ylide rearrangement duets (Scheme 79).^[132] Clark improved upon these rhodium-catalyzed methods by showing that [Cu(acac)₂] led to higher yields and levels of diastereoselectivity, such as in the rearrangement via oxonium 361 to produce tetrahydrofuranone 362.^[133] Intermolecular and asymmetric insertions of carbenoids into allylic ethers have been reported, but with variable results.^[134] Recently, Davies and Li showed that oxonium ylide rearrangement proceeded with high enantioselectivity and could compete with O_H insertion when donor/acceptor carbenoids and a highly substituted alcohol were used as substrates (Scheme 80).^[135] Thus, treatment of allylic alcohol **364** and donor/acceptor diazo compound 363 with the enantiomerically pure [Rh₂{(S)-dosp}₄] catalyst gave allylic alcohol **366** with good diastereoselectivity and chemoselectivity over the O_H insertion product **367**. The yield and diastereoselectivity could be improved by using the enantiomeric form of the catalyst. The example shown demonstrates that even in a “mismatched” case, the catalyst is capable of dominating the control of the reaction stereochemistry.

Initial forays into catalytic ammonium ylide formation/[2,3] rearrangement were reported by Doyle and involved intermolecular coupling of allylic amines and metal carbenoids.^[127] These reactions also relied on high excess of the allylic amine as solvent, and metal carbenoid dimerization had to be suppressed by slow combination of reagents. An intramolecular reaction to generate cyclic amines was first reported by Clark and co-workers^[136] and later explored by McMills and co-workers.^[137] This method was used to prepare a bicyclic ring system relevant to the synthesis of manzamine alkaloids (Scheme 81).^[136b] Transfer of chirality from the (S)-prolinol building block was quite efficient to generate bicyclic amine **372** in high enantiomeric excess. The stereochemistry and conformation of the ylide is inferred from the product observed.^[138]

Hodgson and co-workers demonstrated that ylide formation sequences could be combined in one-pot processes with alkene cross-metathesis reactions.^[139] For example, they reported a consecutive reaction trio involving a cross-metathesis/oxonium ylide formation/[2,3]-sigmatropic rearrangement to access dihydrofuranones with high diastereoselectivity. Thus, α -diazo- β -ketoesters such as **373** were first treated with Grubbs II catalyst and a substituted alkene, followed by addition of a catalytic amount of rhodium(II) acetate (Scheme 82). Because of instability, the final aldehyde was immediately treated with sodium cyanoborohydride to give hemiketal 377 as an 80:13:4:3 mixture of diastereomers in favor

of the desired isomer shown. The observation of allylic transposition indicates that a pericyclic [2,3]-sigmatropic rearrangement pathway is likely.

In exploring ways to functionalize the C5 position of dpyrones, de March and co-workers utilized a [2,3]-sigmatropic rearrangement of sulfonium ylides in two separate reaction trios.^[140] When the parent phenylthiomethyl pyrone (**378a**, **X = H**) was treated under rhodium catalysis in the presence of two equivalents of dimethyl diazomalonate, ylide formation was followed by [2,3]-sigmatropic rearrangement (Scheme 83). Under the reaction conditions, the exocyclic double bond did not isomerize to form the fully conjugated pyrone, and so underwent a cyclopropanation with dimethyl diazomalonate. Approach of the carbenoid from the less hindered side led diastereoselectively to spirocycle **382**. Cyclopropanation could be avoided by using a single equivalent of dimethyl diazomalonate. Conversely, if the bromine analogue was used (**378b**, **X = Br**), the exocyclic double bond participated in a [1,3] bromine allylic rearrangement that resulted in the formation of conjugated pyrone **383**.

The groups of Hoye^[141] and Padwa^[13] both combined ylide

formation/[2,3]-sigmatropic rearrangement with rhodiumcatalyzed carbene/alkyne metathesis in a number of related reaction trios. Both groups showed that α -diazo ketones bearing tethered alkyne units isomerize under rhodium catalysis to vinyl metal carbenoids (e.g. **385**, Scheme 84). These intermediates could be trapped and used in a number of tandem reactions to provide substituted cyclopentenones. Oxygen and sulfur ylide representatives of the cyclization/ylide formation/[2,3]-sigmatropic rearrangement trio are shown in Scheme 84. As a probe for the mechanism, Hoye used trapping with external sulfides to identify isomeric carbene intermediates resulting from alkyne insertion (not shown).

A recent report demonstrated an alternative to the general practice of independently preparing diazo compounds for use in the tandem ylide formation/[2,3]-sigma-tropic rearrangement sequence. Murphy and West^[142] reported that β -ketoesters with pendant allyl or benzyl ethers or sulfides could be converted in a one-step sequence to cyclic ethers and sulfides. Treatment of β -ketoesters **388a** and **388b** with phenyl iodonium acetate, cesium carbonate, and rhodium acetate catalyst provided 2-substituted hetero-cycles **391a** and **391b**, presumably via ylide **390** (Scheme 85). For many of the substrates examined, the yields of this reaction trio were competitive with those obtained by the corresponding two-step diazo preparation/carbene-transfer rearrangement sequence (68% and 55% yields respectively for **388a** and **388b**). For allyl substrates, the Stevens [1,2] shift was not ruled out.

Ohe and co-workers showed that related vinyl metal carbenoids could be generated by the cyclization of carbonyl compounds onto tethered alkynes, in a process that precludes the need to independently prepare precursor diazo compounds. Enyne carbonyl compounds, such as **392**, in the presence of catalytic rhodium(II) acetate, cyclized to generate an intermediate metal carbenoid (Scheme 86). For example, in the presence of alkenes, cyclopropane products were isolated that are consistent with such presumed carbenoids. In the presence of sulfides however, a Doyle–Kirmse-type reaction, or ylide formation/[2,3]-

sigmatropic rearrangement, occurred. When performed in the presence of a bisallylic sulfide, a reaction quartet was observed that terminated by an intramolecular Diels–Alder reaction, leading to significantly more complex products, such as **397**.^[143]

Onium ylides can be generated using gold catalysts, as demonstrated by the rearrangement quartet reported by Davies and Albrecht.^[144] The reaction is initiated by the gold-catalyzed [1,2] migration of propargyl esters, such as **398** (Scheme 87).^[69] A postulated gold carbene is generated that can be captured by an allylic sulfide to generate free (or gold-bound) ylide **401**. Following [2,3] rearrangement, diene **402** is then poised to undergo Cope rearrangement to produce enol acetate **403** in excellent yield.

If an allyl propargyl sulfide is used, an alternate rearrangement quartet occurs. The previously described ylide formation/[2,3] rearrangement proceeds to presumably generate enyne **406** (Scheme 88).^[144] Gold catalyst activation of the alkyne then leads to a carbothiolation and [3,3] rearrangement, similar to that shown in Scheme 63, to generate dihydrothiophene **408**. Mechanistic understanding of these types of cycloisomerizations is still evolving.

Tambar and co-workers sought to expand the chemistry beyond diazo compounds for the catalytic generation of ammonium ylides by exploring allylic substitution methods, and recently reported a palladium-catalyzed method involving alkylation of tertiary amines for the generation of ammonium ylides for [2,3] rearrangement.^[145] In the first example of the use of tertiary amines as intermolecular nucleophiles in metal-catalyzed allylic substitutions, they showed that carbonates such as **409** could be treated with amines in the presence of [Pd₂dba₃], phosphine, and base to afford homoallylic amines such as **412** in good yields and high diastereoselectivity (Scheme 89). Mechanistic studies suggest that formation of the unstable ammonium intermediate is unfavored, but followed by rapid deprotonation and rearrangement, thus explaining the challenges associated with previous attempts to invoke tertiary amines in allylic alkylation. Tambar also developed asymmetric [2,3] rearrangements of sulfimides and amine-N-oxides, as noted below.

3.2. “Heteroatom Ylides”

In their program to develop new tandem cycloadditions utilizing 1,3 dipoles, Grigg and Markandu explored the in situ generation of nitrones by the [2,3]-sigmatropic rearrangement of *O*-allyl ethers of oximes.^[146] However, thermal conditions afforded low yields of the products of [2,3]-sigmatropic rearrangement/dipolar cycloaddition duets (Scheme 90).

The reaction was much more successful when catalyzed by palladium. Treatment of *O*-allyl ether oxime **413** and **417** with catalytic bis(acetonitrile) dichloropalladium provided bicycle **416** and tricycle **419** from trapping of intermediate nitrones. The lower yield of the latter reaction was attributed to the potential reactivity of aryl allyl ethers with palladium(II) to also form π -allyl species.

A similar reaction that does not involve the generation of reactive intermediate ylides is the [2,3]-sigmatropic rearrangement of sulfinates. This rearrangement was used by Mukai and co-workers in a reaction duet for the in situ preparation of a phenylsulfonyl allenyne

Pauson–Khand substrate (Scheme 91).^[147] Treatment of propargyl sulfinate ester **420** with a rhodium(I) catalyst gave cyclopentindenone **422**, which was presumed to arise through carbonylative [2+2+1] ring-closing reaction of phenylsulfonyl allenyne **421**. Interestingly, thermal [2,3] rearrangement was unsuccessful, suggesting that rhodium catalysis is in effect. These structures were targeted as possible intermediates in the synthesis of cyanosporasides.

The Mislow–Evans rearrangement is a commonly used strategy to prepare allylic alcohols (type II, Scheme 77). It involves the [2,3]-sigmatropic rearrangement of allylic sulf-oxides and is frequently performed as a single-pot reaction trio combining oxidation of a sulfide to a sulfoxide, followed by thermal rearrangement and cleavage of the resultant sulfenate. These sequences are rarely catalytic. However, in a selenium analogue of the Mislow–Evans rearrangement, Carter and Bourland showed that aryl selenides such as **424** could be oxidized to the corresponding selenate using catalytic vanadium(IV) acetylacetonate (Scheme 92).^[148] Stoichiometric amounts of cumene hydroperoxide reoxidized the vanadium and a final tri n-butyl phosphine quench cleaved the O–Se bond to generate an allylic alcohol, thus completing this reaction trio sequence. Oxidation under Sharpless asymmetric conditions could also be used to asymmetrically generate selenoxides, ultimately leading to enantiomerically enriched allylic alcohols, however the latter reaction trio could not be accomplished catalytically.^[149] Related two-pot stoichiometric oxidation/catalytic asymmetric [2,3] rearrangement of amine-N-oxides was recently reported by Tambar and co-workers.^[150]

Similarly, the [2,3] rearrangement of allyl sulfimides constitutes a nitrogen analogue of the Mislow–Evans rearrangement. Sulfimides can be generated catalytically to initiate tandem rearrangement sequences. In a report by Murakami and Katsuki, use of an enantiopure ruthenium(II) complex initiated an asymmetric rearrangement trio that was terminated by basic hydrolysis to generate enantiomerically enriched allylic amines.^[151] Thus, treatment of allylic sulfide **357** with tosyl azide, molecular sieves, and [(CO)Ru(salen)] catalyst **431** led initially to sulfimide **428** (Scheme 93). Rearrangement gave sulfonamide **429**. Basic cleavage of the nitrogen sulfur bond afforded allylic amines of type **430** in good yields and enantiomeric excess. This transformation is an improvement on a copper-catalyzed sulfimide formation rearrangement duet.^[152] Iron(II) is also a competent catalyst.^[153] Two-pot sulfimide formation/[2,3] rearrangements were recently reported in a catalytic, enantioselective fashion by Tambar and co-workers.^[154]

A catalytically initiated tandem sequence that has been frequently utilized in total synthesis is the Knoevenagel reaction/Mislow–Evans rearrangement originally reported by Nokami.^[155,156] Although the Knoevenagel reaction is typically induced with a stoichiometric amount of amine, the amine is a chemically catalytic reagent. A recent example of this reaction quartet utilized the solid support N,N-diethylaminopropylated silica gel (NDEAP) as a stable and recoverable catalyst (Scheme 94).^[157] Knoevenagel reaction between citronellal and arylsulfinylacetonitrile **433** generated a vinyl sulfoxide that was in equilibrium with allyl sulfoxide **435**. [2,3]-Sigmatropic Mislow–Evans rearrangement and sulfenate cleavage generated allylic alcohol **437** as a mixture of diastereomers. The Knoevenagel reaction can itself be considered a reaction duet: aldol addition followed by

dehydration. Perhaps the aforementioned sequence would be more appropriately called a reaction quintet!

4. Miscellaneous [X,Y] Rearrangements

A number of other [X,Y]-sigmatropic rearrangements are thermally and photochemically allowed; however, their involvement can be more difficult to detect and distinguish from simple proton-transfer processes. Additionally, they often occur under similar conditions and in competition with other rearrangements, and rarely exist independently as distinct, selective processes. They do however represent an important area of exploration. In Scheme 38 and 48, the [1,3] rearrangement from oxygen to carbon was a competing process in Claisen rearrangements, and Rovis and Nasveshuk, for example, specifically explored optimizing it for use in stereoselective synthesis.^[158] Only a few catalytic examples in tandem reactions are presented here.

With substrates related to those in Scheme 78–80, but lacking the pendant olefin, ammonium ylides can be generated from cyclic amines (**439**, Scheme 95). Spirocyclic intermediates then undergo [1,2] shift, also known as the Stevens rearrangement, with concomitant ring expansion. The groups of Padwa, Saba, and West each utilized such a duet to prepare fused bicyclic frameworks.^[159]

In an effort to expand the chemistry of metallonitrenes into the broader realm of reactions such as those displayed by analogous metallocarbenes, Thornton and Blakey reported a metallonitrene/alkyne metathesis reaction quartet.^[160] Thus, treatment of simple linear sulfamate ester (**441**) with phenyl iodonium acetate and a rhodium(II) catalyst followed by reductive workup provided good yields of bicyclic oxathiaze-panes (**447**, Scheme 96). The sequence is believed to proceed by alkyne attack on an electrophile rhodium nitrene leading potentially to a vinyl cation that isomerizes to an imine metallocarbene (**443**). The metallocarbene can then be captured by the pendant allyl ether to generate an ylide (**444**) that is poised for a sigmatropic rearrangement, likely a [1,2] rearrangement, since benzyl ethers are also competent. Although the resultant N-sulfonyl imines could be isolated, they were sensitive to hydrolysis upon purification. It was shown to be operationally convenient to reduce them in situ or capture them with an organometallic reagent in reactions that produce a single diastereomer.

Under platinum catalysis, Liang and co-workers observed a [1,5] shift that followed [3,3] propargylic ester rearrangement (a process discussed in Section 2.2.3).^[161] Specifically, propargylic ester **448** was proposed to first rearrange to allenyl ester **449** (two diastereomers possible, Scheme 97). A [1,5] shift leads to the formation of triene **450**, which then undergoes 6p cyclization to give naphthyl acetate **451**.

In their work on the synthetic elaboration of N-protected bromomethylindoles, Mohanakrishnan and co-workers reported a ZnBr₂-mediated arylation/[1,5]-sigmatropic rearrangement trio.^[162] The domino sequence was initiated by the zinc(II)-mediated arylation of bromomethylindole **452** with anisole, a reaction that likely proceeds through a Friedel–Crafts-type mechanism, and so is included under our umbrella definition of catalysis (Scheme 98). A [1,5]-sigmatropic shift gave hexatriene **455**, which then underwent

a 6p electro-cyclization. Elimination of malonate with rearomatization provided the annulated product **457**.

Expanding on their work with rhodium carbenoids (see also Scheme 2 and Scheme 80), Davies and co-workers explored catalytic enantioselective C–H activations. Reactions involving dienes and vinyl diazoacetates resulted in nonconjugated products, revealing a new mechanistic process, the C–H activation/Cope rearrangement (for example **458** and **459** to **460**, Scheme 99).^[163] On its own, it is not a reaction duet, but rather a new reaction type that combines C–H activation with Cope rearrangement in a concerted process (see scheme for the proposed transition state). In the reaction of naphthalenes with phenyl-substituted vinyl diazoacetate **363**, the reaction is followed by a retro-Cope rearrangement to form **462**, the expected product of direct C–H insertion.^[163b] The much higher diastereoselectivity observed compared to other direct C–H insertions provided evidence for this “hidden” reaction duet. Davies demonstrated the utility of the C–H activation/Cope rearrangement in total synthesis.^[163c] The novel process is another hint of the exciting possibilities that still remain in synthetic chemistry for harnessing new types of reactivity.

5. Outlook

Although the reactions presented herein range from the very simple to the very complex, they were each made possible and became more versatile when chemists combined a strong mechanistic understanding of reactivity and selectivity with a consideration of possible influences in more complicated systems. Oftentimes, great successes result from an appreciation for and the pursuit of “unexpected” products. It is in such by-products that tandem processes are often revealed. As chemists strive for increasing levels of control, for each catalyst or reagent to accomplish more, advancement will surely depend upon both artistic creativity in substrate design and systematic mechanistic analysis. By using tandem reactions, we should be able to engineer contexts where multiple pathways are possible, but only the desired pathway proceeds. In some cases, this will involve a multitude of compatible reagents carrying out different processes; in others, the catalysts themselves will prove capable of mediating multiple different processes, as in “concurrent catalysis.”^[164] Such total understanding of conformational elements, reaction selectivity, and catalyst compatibility would allow us to engage a single simple substrate and direct it to rearrange by a specific reaction sequence to the complex product of choice. Although outside the scope of our review, we take inspiration from the Heathcock syntheses in the daphniphyllum alkaloid series, where by judicious choice of starting material resulted in the molecule curling upon itself to assemble a structure mere steps away from the desired natural product.^[165] As catalyst activity and control of selectivity in cascade processes becomes even better and more routine, synthetic chemists will have unprecedented success in creating intricate structures in only a few steps and with extreme efficiency.

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Biography



Amanda C. Jones was born in Evanston, IL in 1979. She obtained an A.B. in chemistry from Princeton University in 2001 where she worked with Maitland Jones, Jr. In 2007, she obtained her Ph.D. from the University of Wisconsin under the direction of Hans J. Reich. She was an NIH postdoctoral scholar with Brian M. Stoltz from 2007–2010. In 2010, she started her independent career at Wake Forest University, where her research is focused on mechanistic organometallic chemistry and NMR spectroscopy.



Jeremy A. May was born in Bozeman, MT in 1975. He obtained his B.S. in chemistry from the University of Utah in 2000 where he worked for Peter Beal. In 2006, he obtained his Ph.D. from Caltech under the direction of Brian M. Stoltz. He was an NIH postdoctoral fellow in the group of Samuel J. Danishefsky at the Memorial Sloan Kettering Cancer Center from 2005– 2008. In 2008, he began his independent career at the University of Houston, where his research is focused on natural product synthesis and methods development related to unsaturated and low-valent carbon.



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Brian M. Stoltz was born in Philadelphia, Pennsylvania, USA in 1970. He obtained his B.S. in Chemistry and B.A. in German from Indiana University of Pennsylvania in 1993. In 1997, he earned his Ph.D. under the direction of Professor John L. Wood at Yale University, specializing in synthetic organic chemistry. Following an NIH postdoctoral fellowship with Professor E. J. Corey at Harvard University (1998–2000), he joined the faculty at Caltech in 2000. His research focuses on the synthesis of complex molecules with important biological properties and the development of new synthetic methods including asymmetric catalysis and cascade processes.

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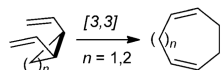
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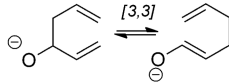
2. [3.3] Rearrangements

2.1. Cope Rearrangement

• 2.1.1. Strain-Release Cope



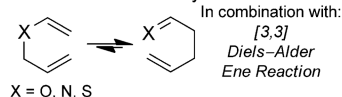
• 2.1.2. Oxy-Cope



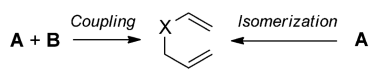
• 2.1.3. Miscellaneous Cope

2.2. Claisen Rearrangement

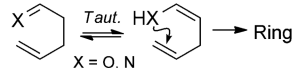
• 2.2.1. Tandem Pericyclic Reactions



• 2.2.2. Metal-Catalyzed Coupling/Claisen and Isomerization/Claisen

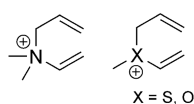


• 2.2.3. Claisen/Cyclization (C-Heteroatom Bonds Formed)



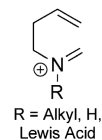
• 2.2.4. Claisen/Coupling (C-C Bonds Formed)

• 2.2.5. Charged-accelerated Claisen



2.3. Cationic Hetero-Cope

• 2.3.1. Aza-Cope



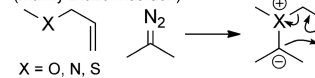
• 2.3.2. Oxonia-Cope



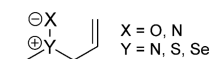
3. [2.3] Rearrangements

• 3.1. Carbon Ylides

(Mainly Diazo Insertion)

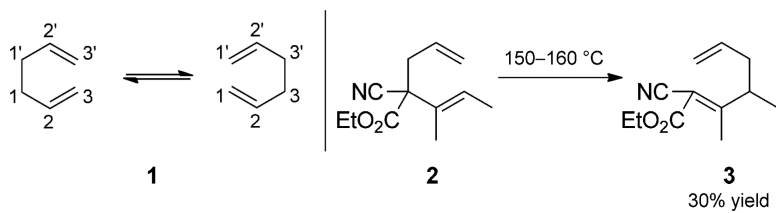


• 3.2. "Heteroatom Ylides"

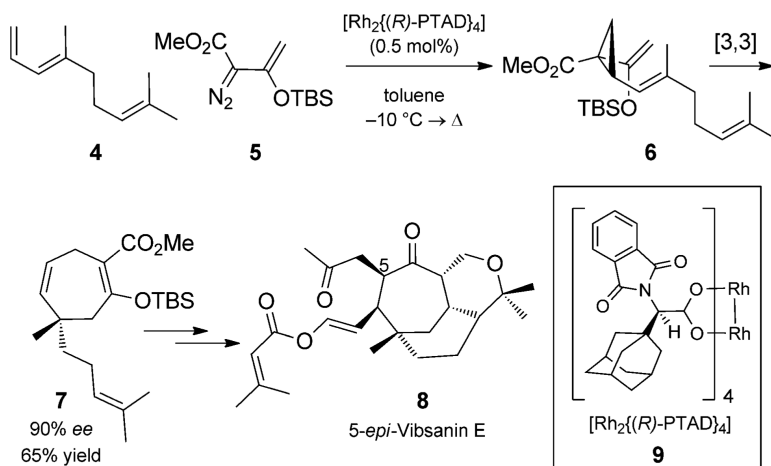


4. Miscellaneous [X,Y] Rearrangements

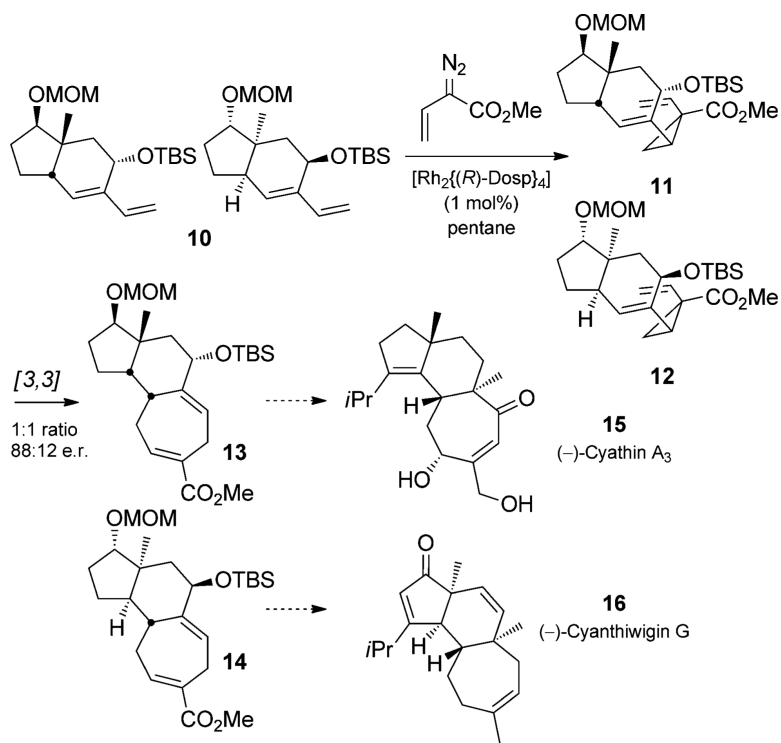
Figure 1.
Graphical overview.



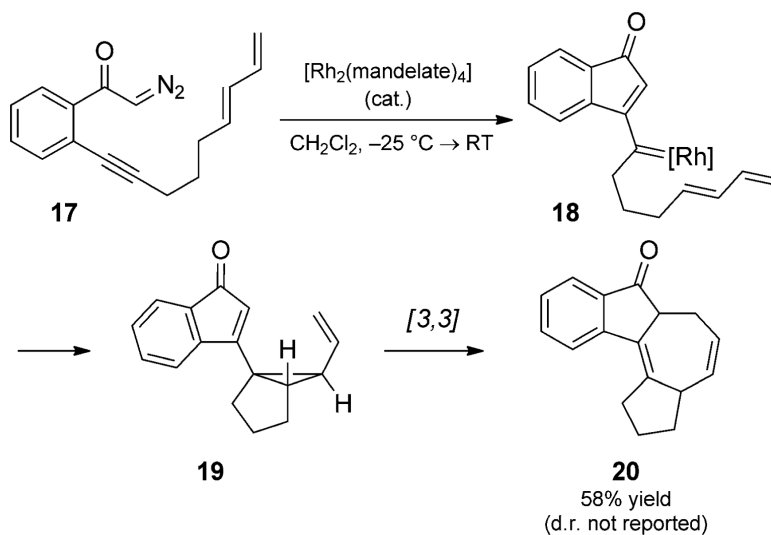
Scheme 1.
Cope rearrangement. [Cope, **1940**, Ref. [5]]

**Scheme 2.**

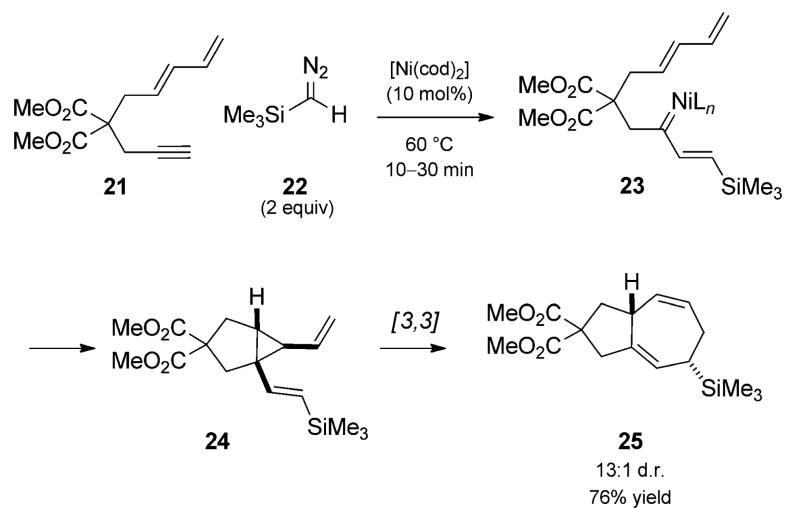
Rhodium-catalyzed asymmetric cyclopropanation/Cope rearrangement duet. [Davies, **2009**, Ref. [10c]]

**Scheme 3.**

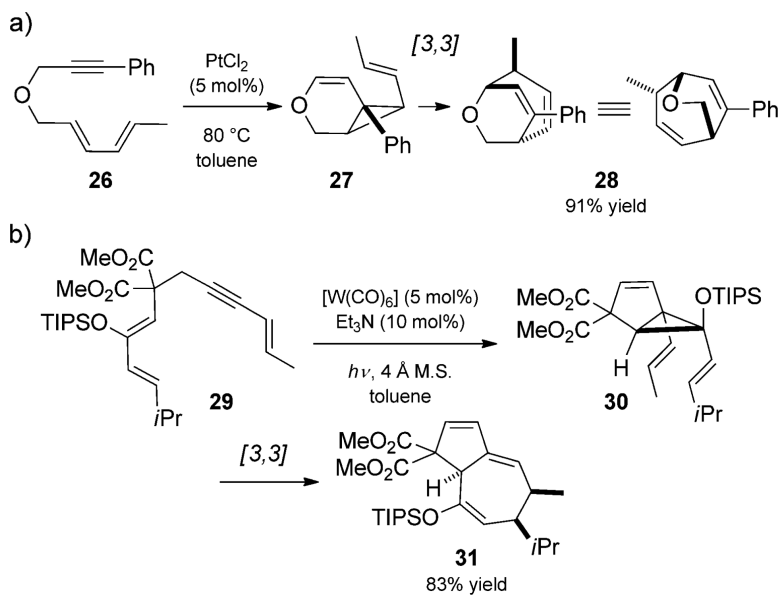
Parallel kinetic resolution using a cyclopropanation/Cope rearrangement duet. Dosp=*N*-[(4-dodecylphenyl)sulfonyl] proline. [Sarpong, **2009**, Ref. [12]]

**Scheme 4.**

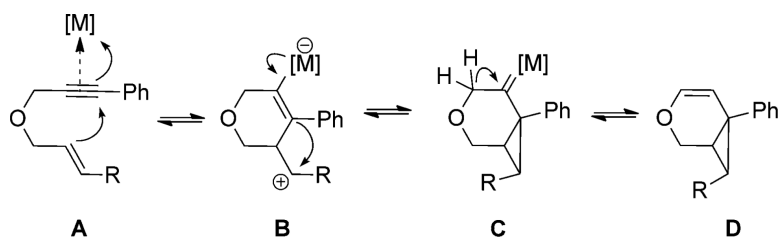
Rhodium-catalyzed alkyne metathesis/cyclopropanation/ Cope rearrangement trio. [Padwa, **1991**, Ref. [13a]]

**Scheme 5.**

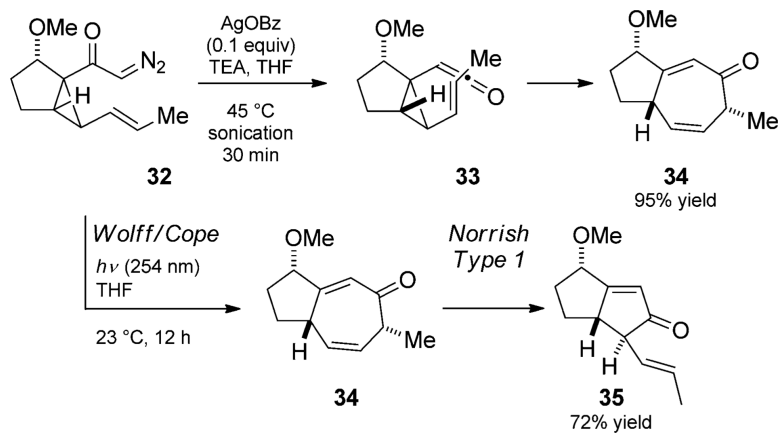
Nickel-catalyzed diazo/alkyne coupling and cyclopropanation/Cope rearrangement trio.
[Montgomery, 2006, Ref. [14]]

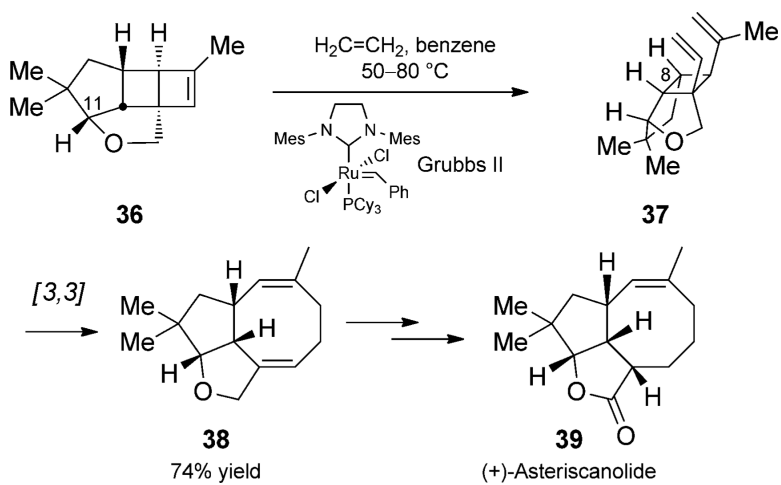
**Scheme 6.**

Enyne cycloisomerization/Cope rearrangement duets postulated to involve divinylcyclopropane intermediates. (a) [Chung, **2010**, Ref. [15a]] (b) [Iwasawa, **2006**, Ref. [15b]]

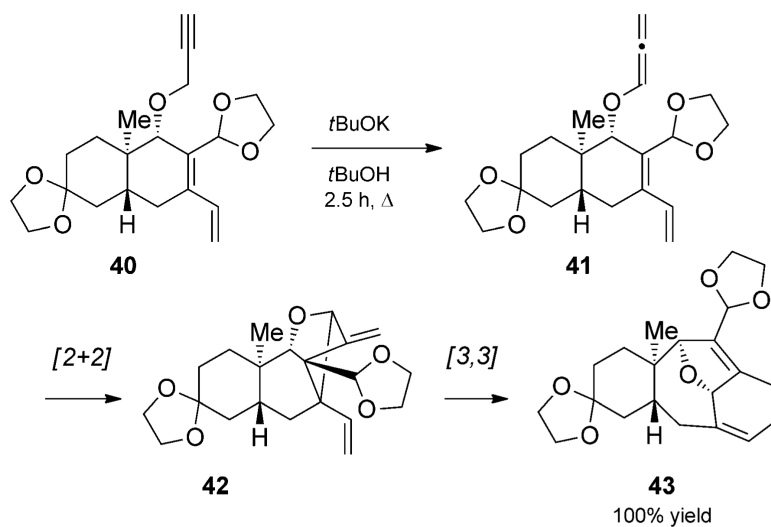
**Scheme 7.**

Proposed mechanism for cyclopropane generation from enynes.

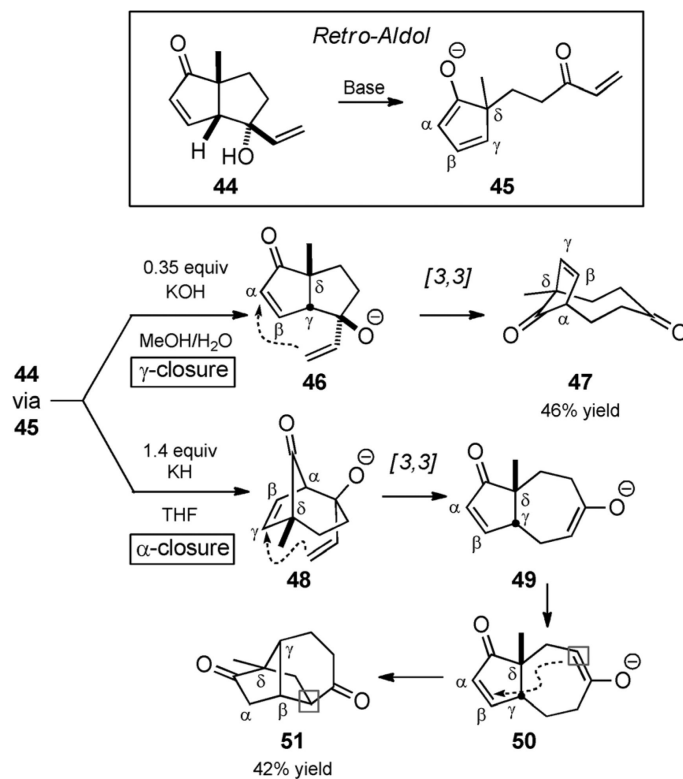
**Scheme 8.**Wolff/Cope rearrangement duet and isomerization trio. [Stoltz, **2003**, Ref. [18]]

**Scheme 9.**

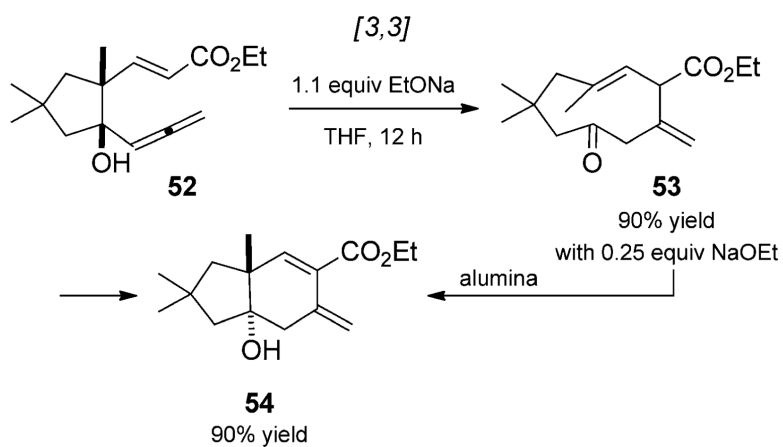
Ruthenium-catalyzed metathesis/Cope rearrangement duet. [Snapper, 2000, Ref. [19]]

**Scheme 10.**

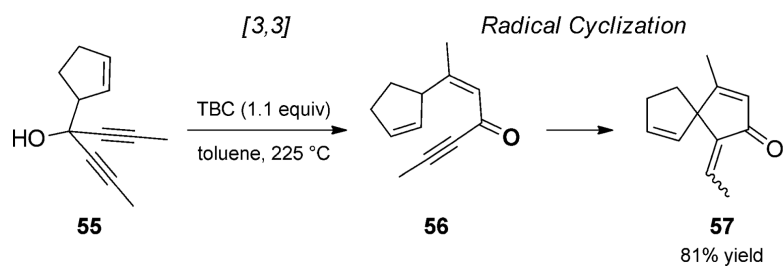
[2+2] Cycloaddition/[3,3] rearrangement trio initiated by base-catalyzed isomerization of a propargyl ether to an allenyl ether. [Kanematsu, 1995, Ref. [20]]

**Scheme 11.**

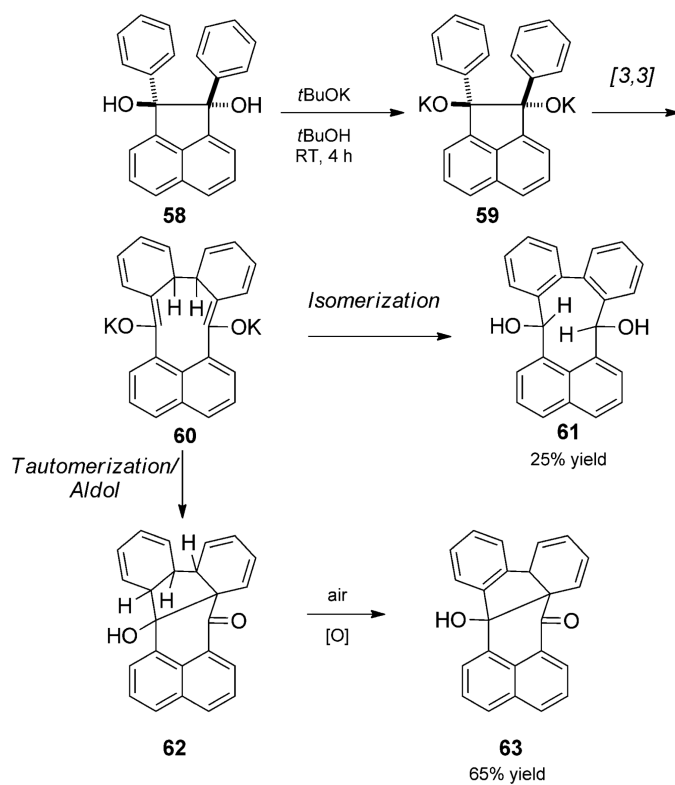
Base-catalyzed oxy-Cope sequences; a retro-aldol/aldol/ oxy-Cope trio and oxy-Cope/ Michael quartet. [Heathcock, **1981**, Ref. [23]]

**Scheme 12.**

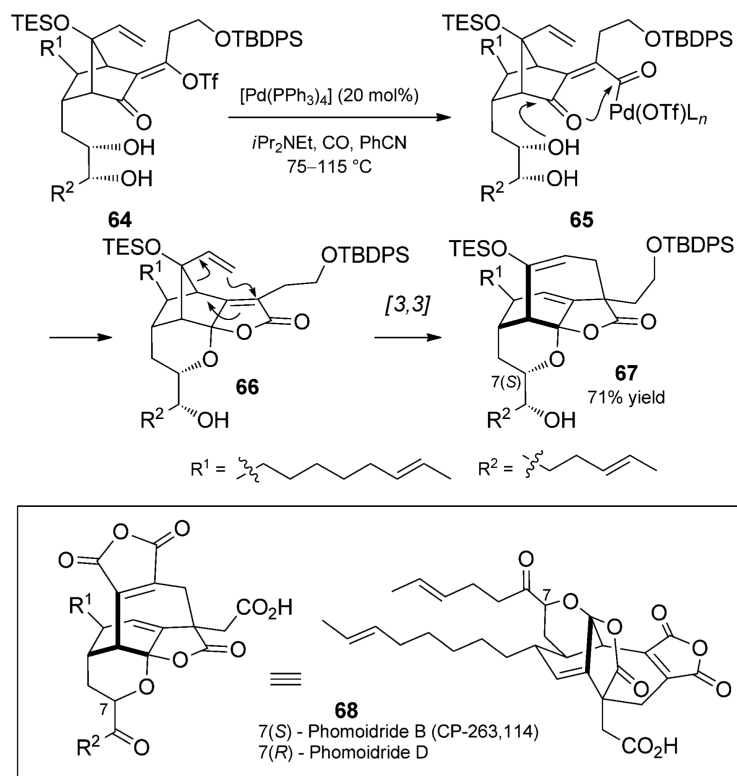
Base-mediated anionic oxy-Cope/aldol reaction duet. [Rajagopalan, 1993, Ref. [24]]

**Scheme 13.**

Phenol-catalyzed electrocyclization preceded by oxy-Cope rearrangement. [Jacobi, **1994**, Ref. [25]]

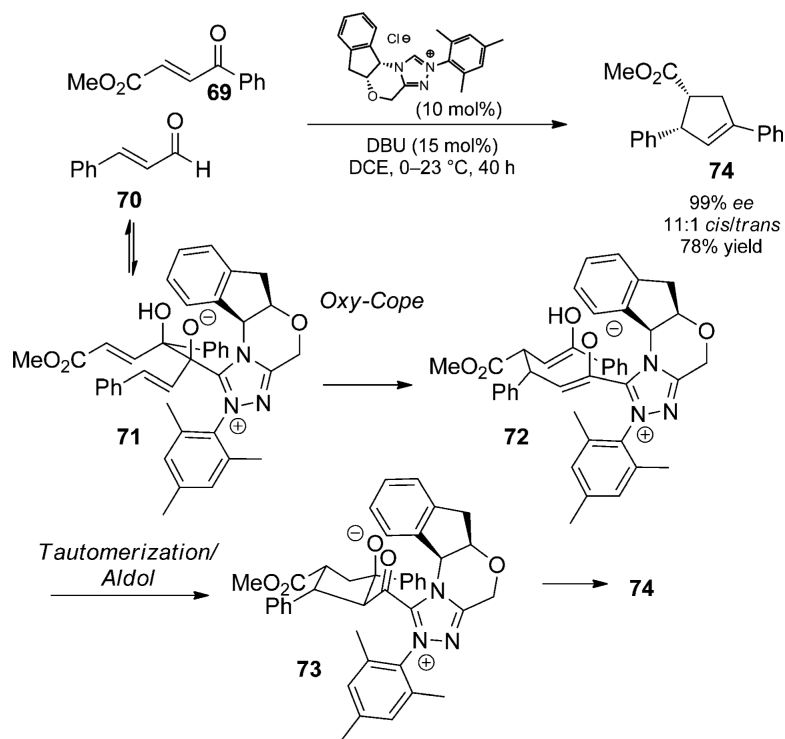
**Scheme 14.**

Base-catalyzed dianionic oxy-Cope rearrangement/aldol/ oxidation trio. [Huq, 2006, Ref. [26]]

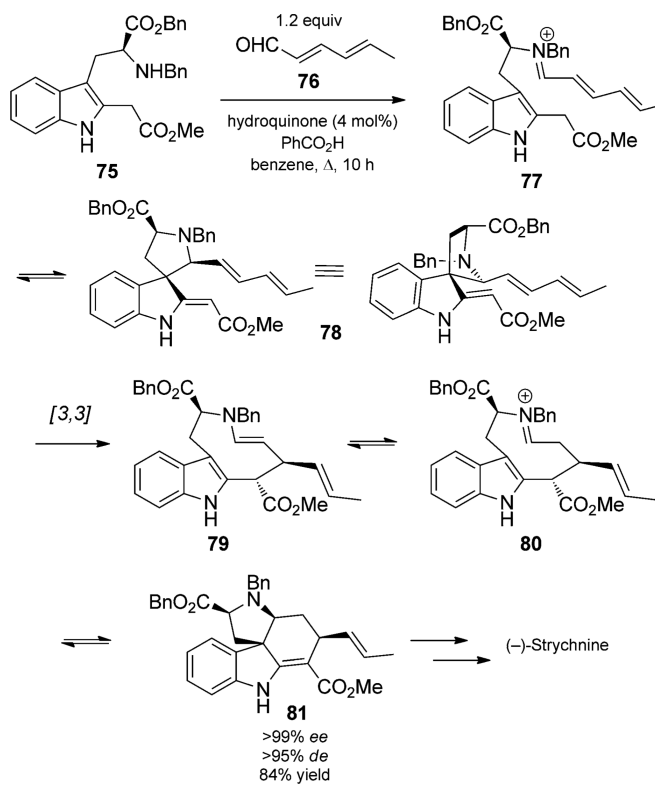


Scheme 15.

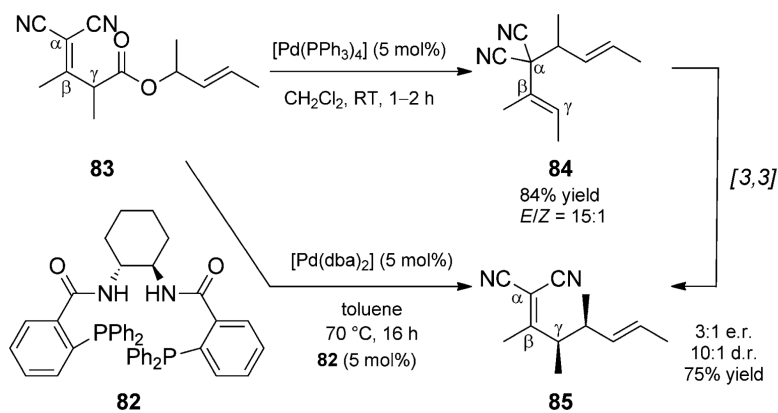
Novel carbonylation strain-release Cope rearrangement duet in the synthesis of phomoidrides. [Leighton, **2003**, Ref. [27a]]

**Scheme 16.**

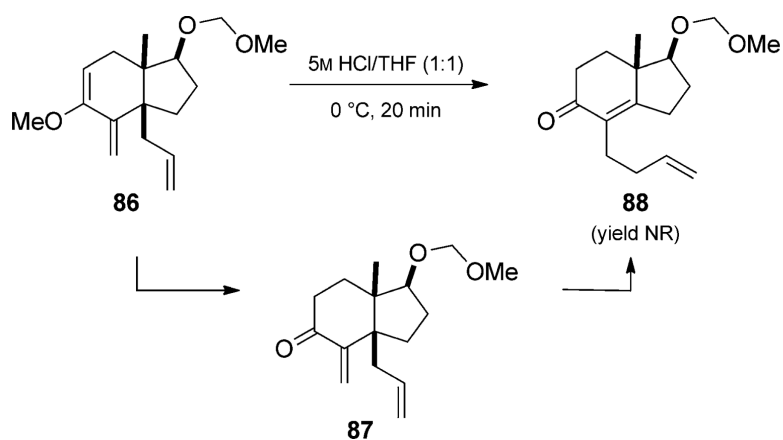
Asymmetric Benzoin-type coupling/cyclization/decarboxylation quartet through oxy-Cope rearrangement catalyzed by an N-heterocyclic carbene. [Bode, **2007**, Ref. [28a]]

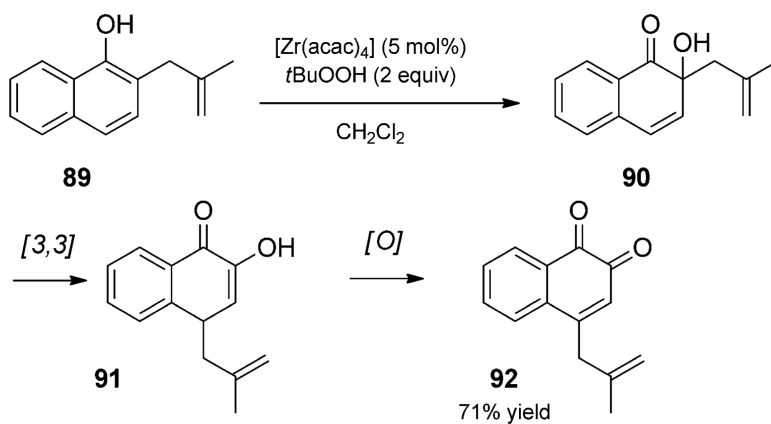
**Scheme 17.**

Diastereoselective Pictet–Spengler/Cope rearrangement trio used in a total synthesis of strychnine. [Kuehne, **1997**, Ref. [29]]

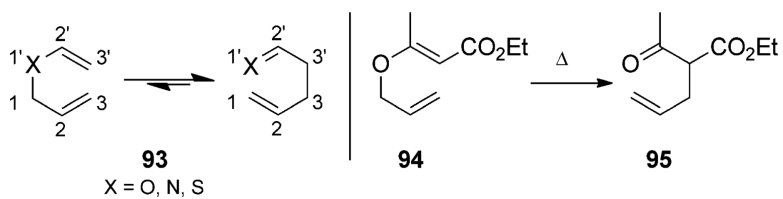
**Scheme 18.**

Palladium-catalyzed decarboxylative coupling/Cope rearrangement duet. [Tunge, 2006, Ref. [30]]

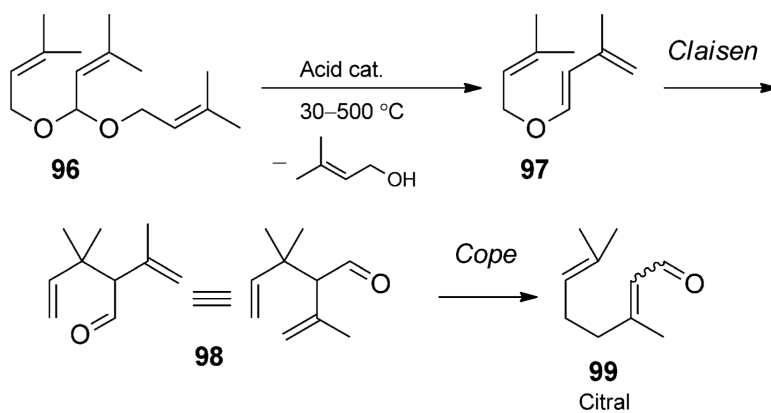
**Scheme 19.**Acid-catalyzed Cope rearrangement duet. [Dauben, **1981**, Ref. [31]]

**Scheme 20.**

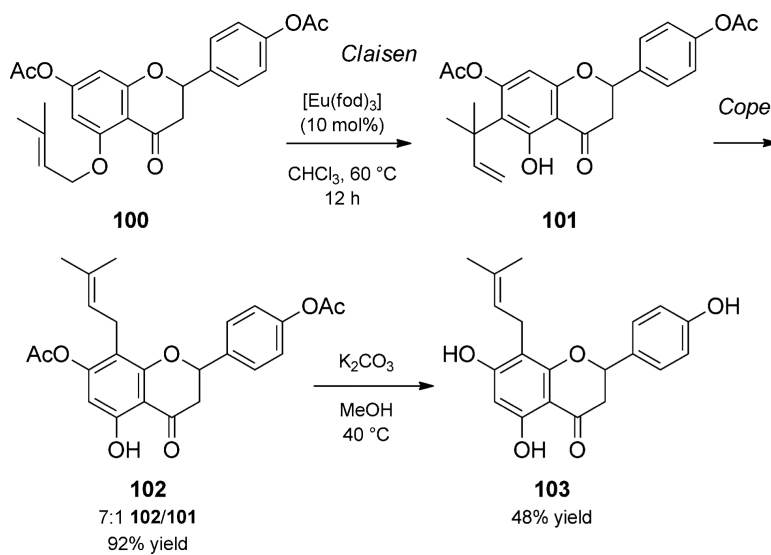
Zirconium-catalyzed oxidation oxy-Cope rearrangement trio. [Krohn, 1996, Ref. [32]]

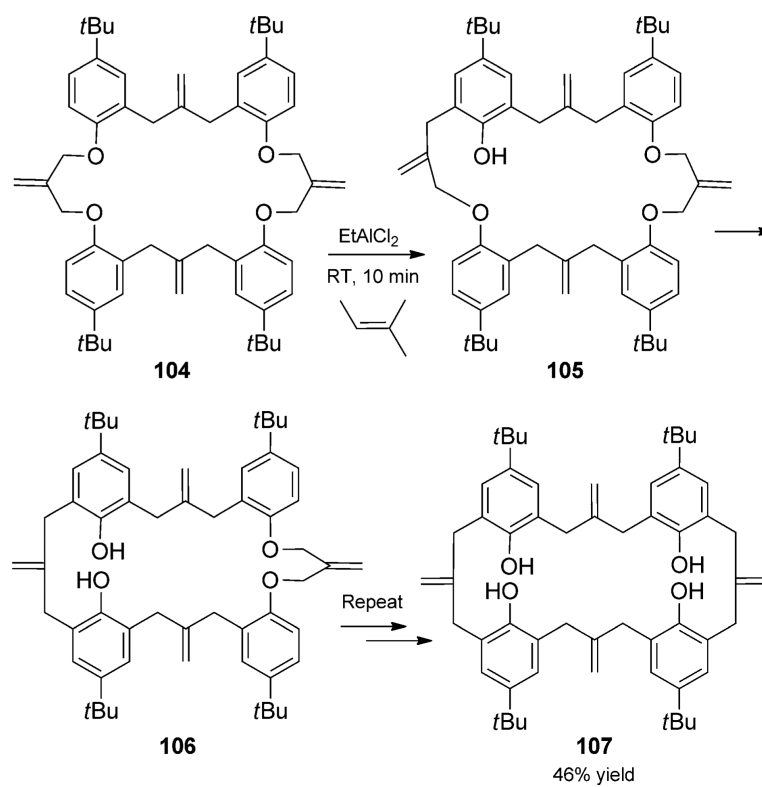
**Scheme 21.**

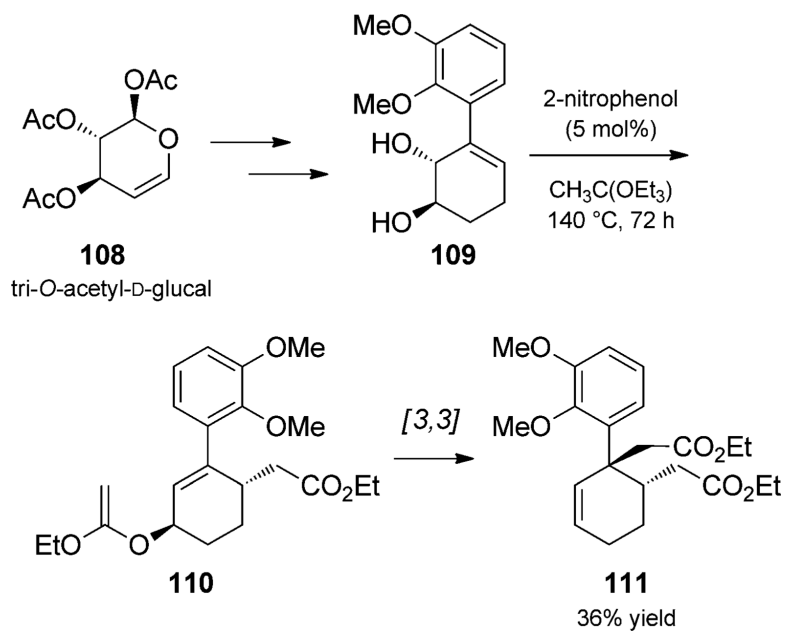
Claisen rearrangement. [Claisen, **1912**, Ref. [33]]

**Scheme 22.**

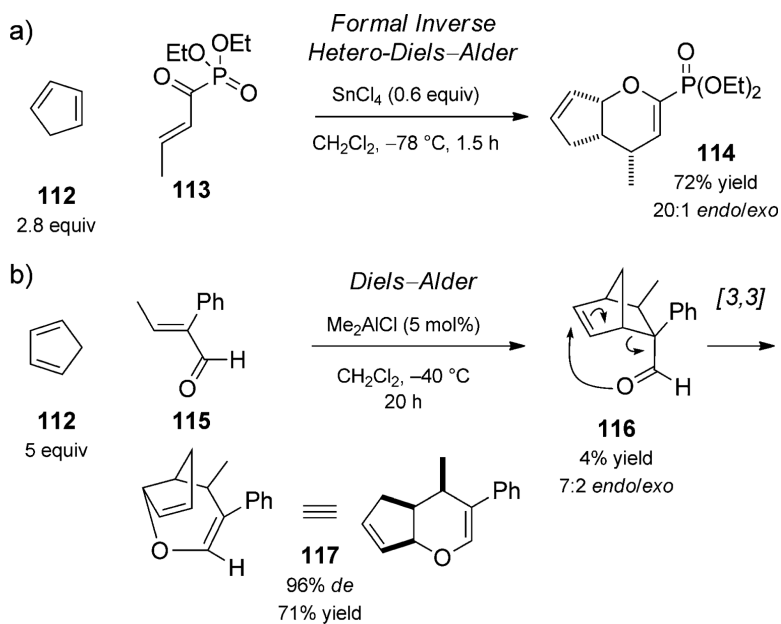
BASF continuous Citral process including a Claisen/Cope rearrangement duet. [1981, Ref. [35]]

**Scheme 23.**Claisen/Cope rearrangement duet. [Metz, **1991**, Ref. [36]]

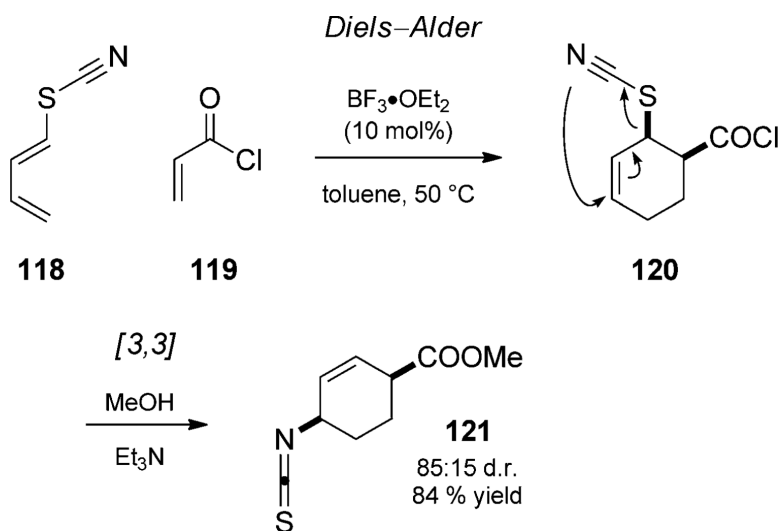
**Scheme 24.**Iterative Claisen rearrangement duets. [Hiratani, **1998**, Ref. [38]]

**Scheme 25.**

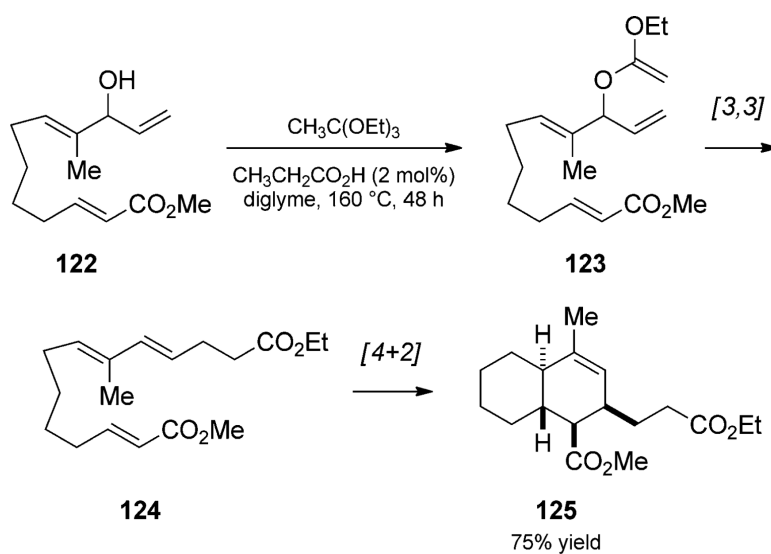
Iterative acid-catalyzed Johnson–Claisen duets. [Chida, 2008, Ref. [39]]

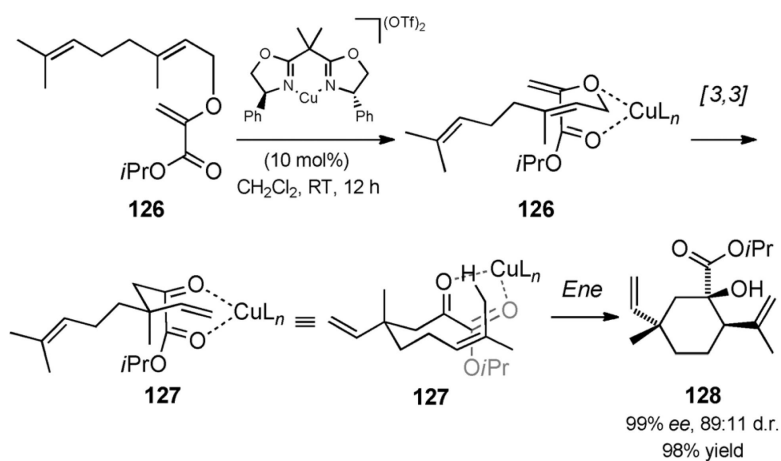
**Scheme 26.**

Lewis acid catalyzed Diels–Alder/retro-Claisen rearrangement duets appear as inverse hetero-Diels–Alder reaction. a) [Hanes-sian, **2002**, Ref. [40]]; b) [Davies, **2005**, Ref. [41]]

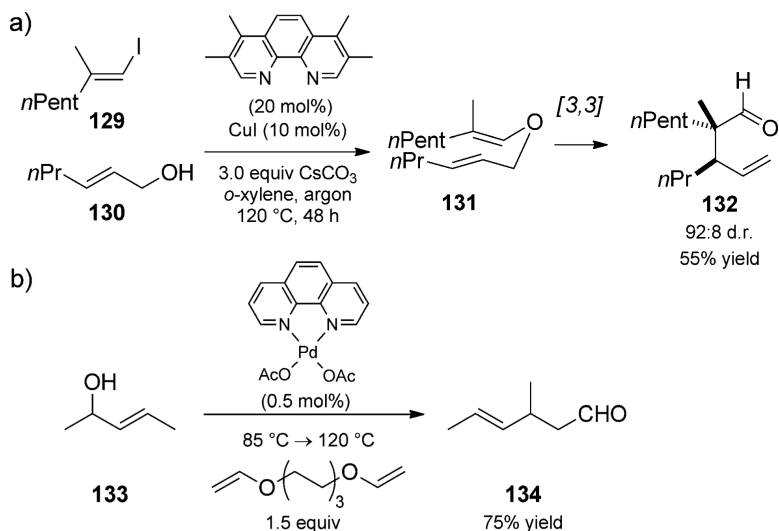
**Scheme 27.**

Lewis acid catalyzed Diels–Alder “hetero-Claisen” rearrangement duet. [Neier, 1994, Ref. [42]]

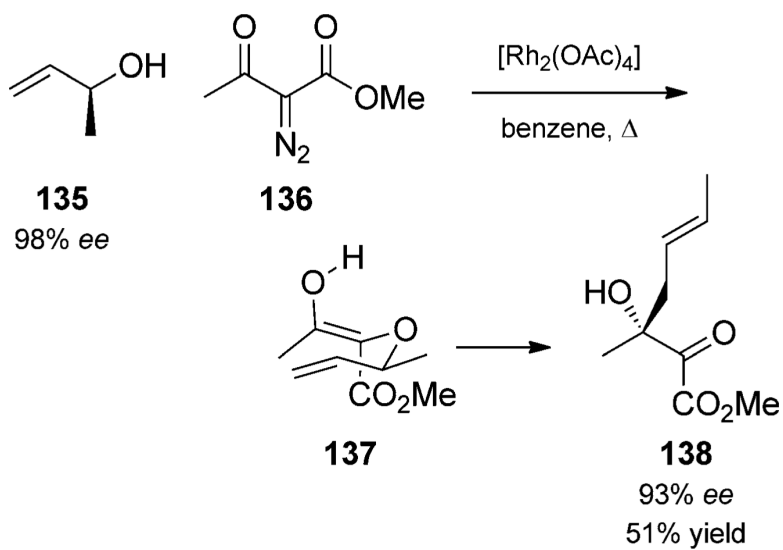
**Scheme 28.**Acid-catalyzed Johnson–Claisen/Diels–Alder cycloaddition trio. [Mulzer, **1991**, Ref. [43]]

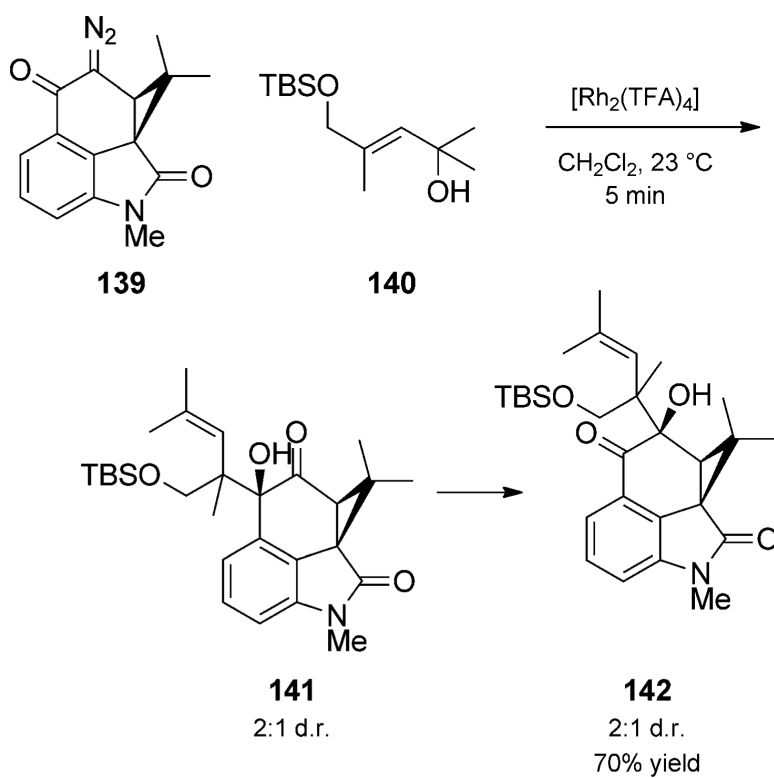
**Scheme 29.**

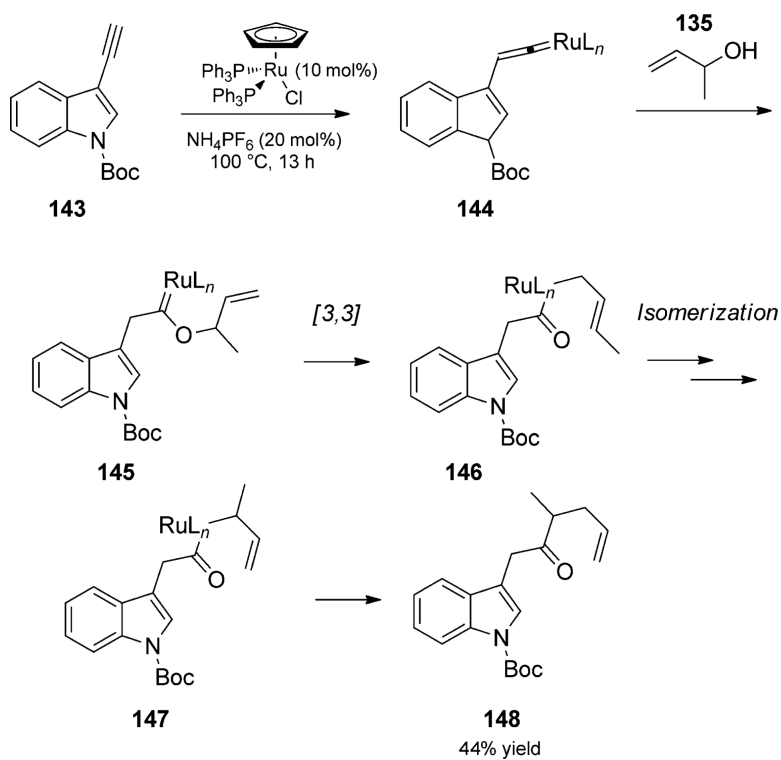
Copper-catalyzed Claisen rearrangement/ene reaction duet. [Hierseman, **2002**, Ref. [44]]

**Scheme 30.**

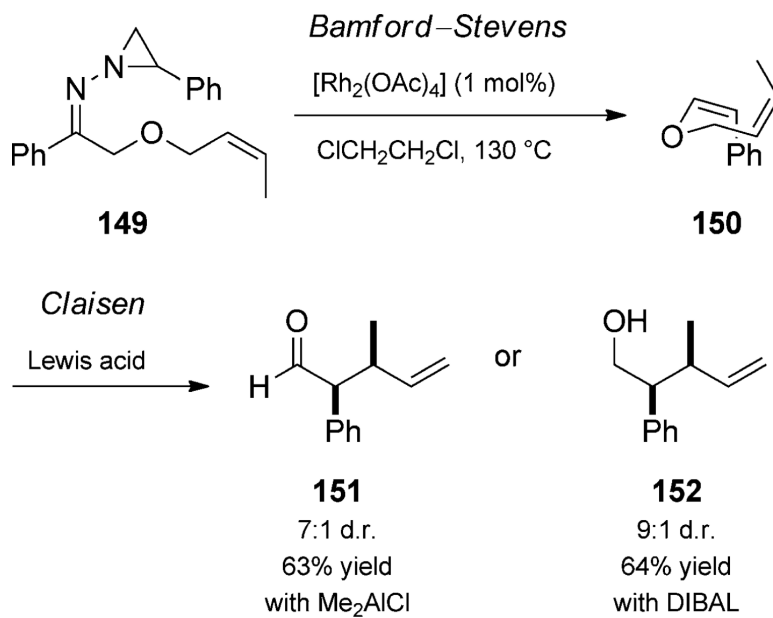
Copper- and palladium-catalyzed alcohol coupling/Claisen rearrangement duets. a) [Buchwald, **2003**, Ref. [46]]; b) [Wei, **2007**, Ref. [47]]

**Scheme 31.**Rhodium-mediated OH insertion/Claisen rearrangement duet. [Wood, **1999**, Ref. [48a]]

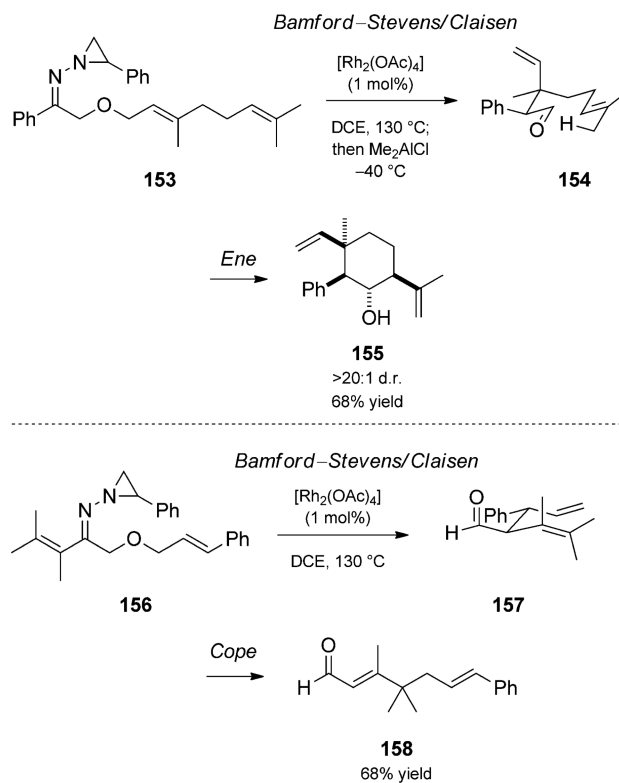
**Scheme 32.**Rhodium-mediated OH insertion/Claisen/ketol rearrangement trio. [Wood, **1999**, Ref. [48c]]

**Scheme 33.**

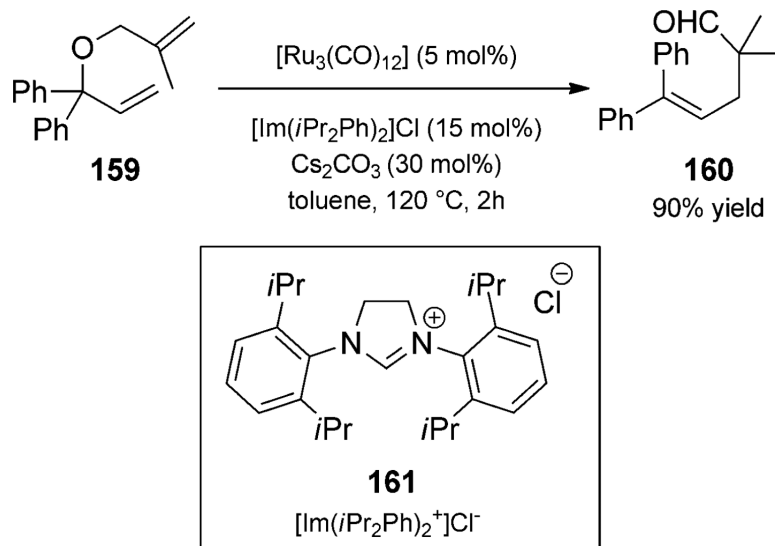
Ruthenium-catalyzed metallo-Claisen rearrangement/coupling duet. [Trost, 1990, Ref. [49]]

**Scheme 34.**

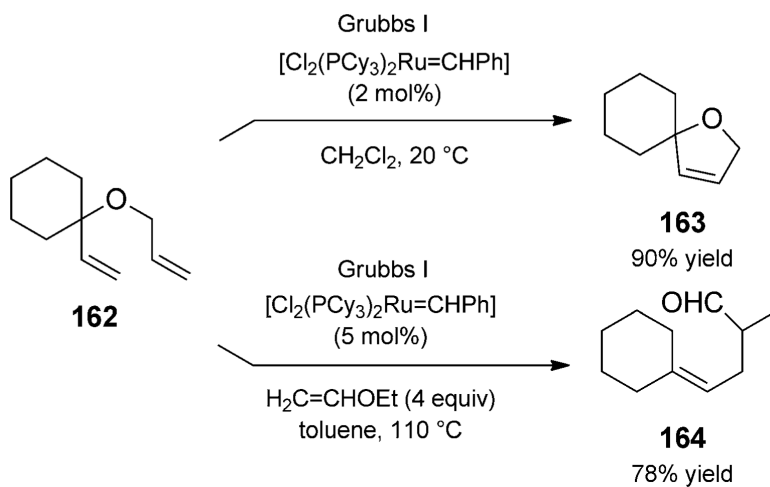
Rhodium-catalyzed Bamford–Stevens/Claisen rearrangement trio and reduction quartet.
[Stoltz, **2002**, Ref. [50]]

**Scheme 35.**

Bamford–Stevens/Claisen rearrangement quartets. [Stoltz, 2002, Ref. [50]]

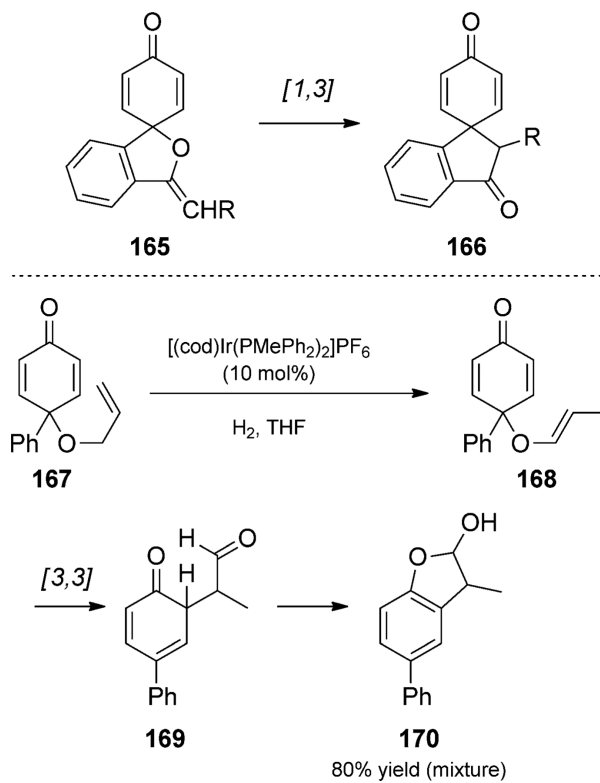
**Scheme 36.**

Ruthenium-catalyzed isomerization/Claisen rearrangement duet. [Dixneuf, 2002, Ref. [52a]]

**Scheme 37.**

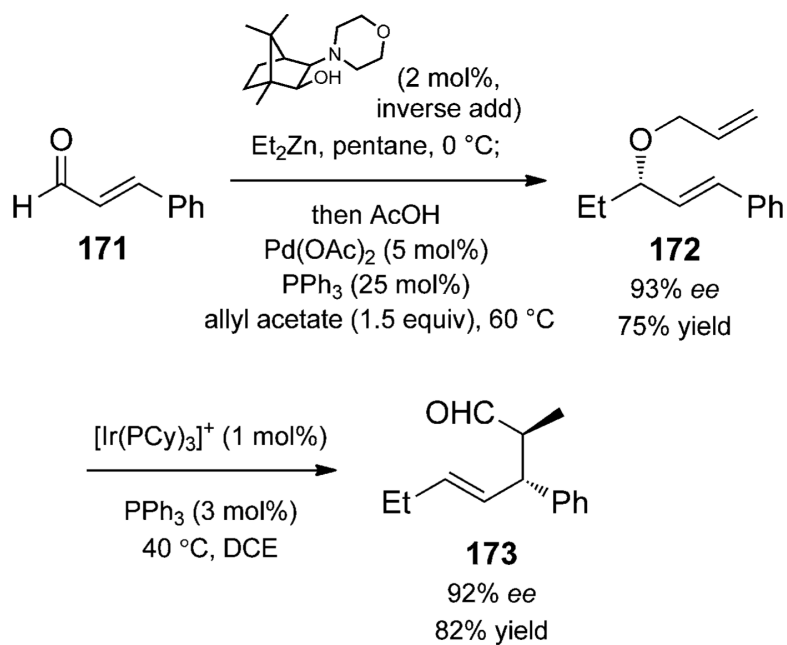
Orthogonal reactivity using Grubbs catalyst; metathesis versus isomerization/Claisen duet.

[Schmidt, **2000/2004**, Ref. [53]]

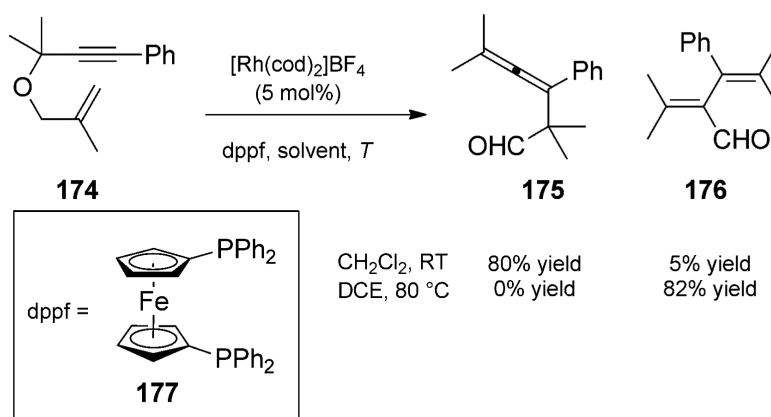
**Scheme 38.**

Iridium-catalyzed isomerization/Claisen rearrangement trio terminated by lactol formation.

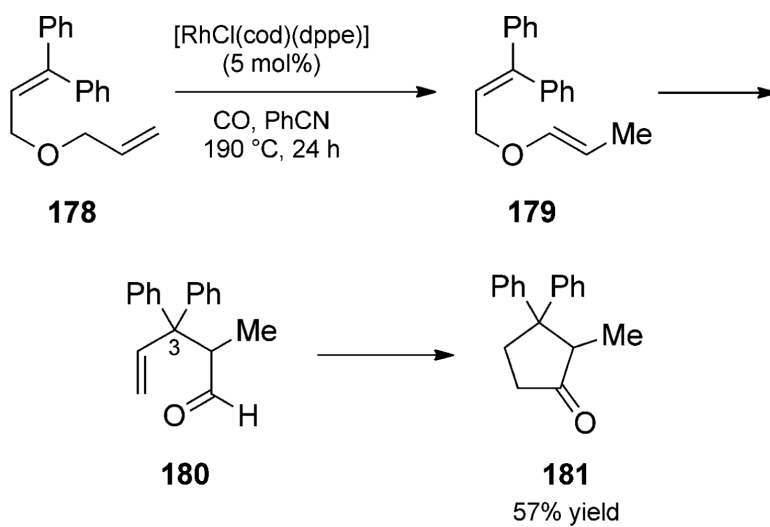
[Swenton, **1991**, Ref. [55]]

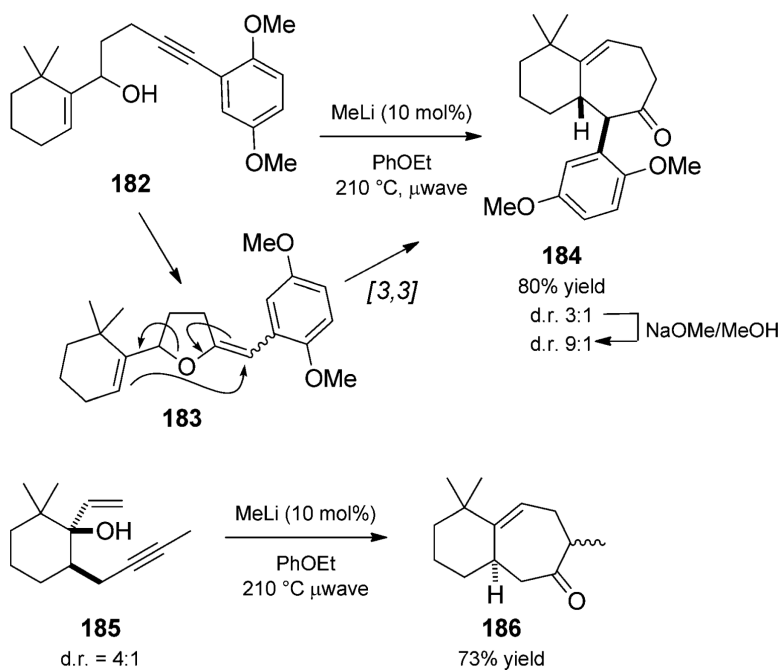
**Scheme 39.**

A consecutive quartet ensemble: asymmetric alkyl zinc addition/palladium etherification duet, followed by isomerization/ Claisen rearrangement duet. [Nelson, **2005**, Ref. [56b]]

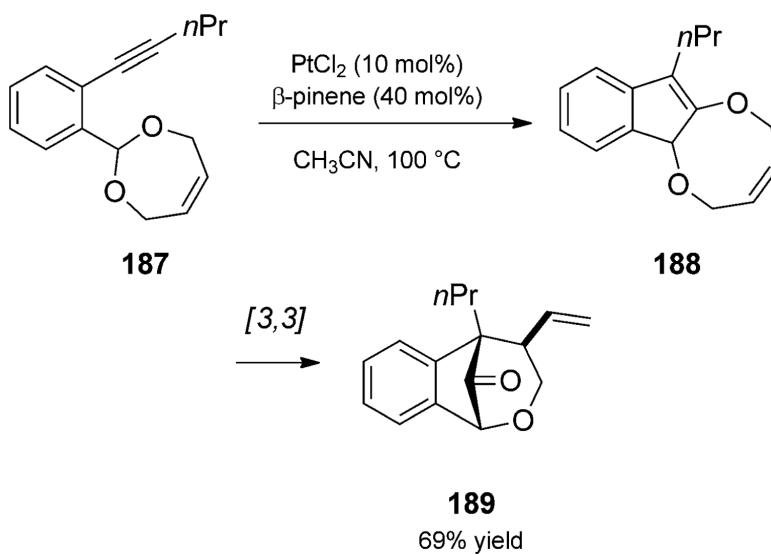
**Scheme 40.**

Rhodium-catalyzed isomerization/Claisen rearrangement duet (to **175**) and migration trio (to **176**). [Tanaka, **2009**, Ref. [57]]

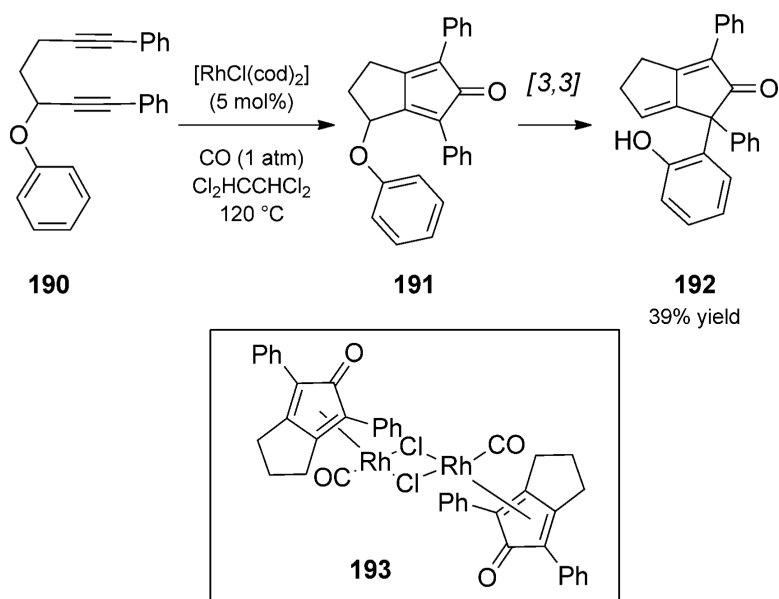
**Scheme 41.**Rhodium-catalyzed isomerization/Claisen/hydroacylation trio. [Eilbracht, **1995**, Ref. [58]]

**Scheme 42.**

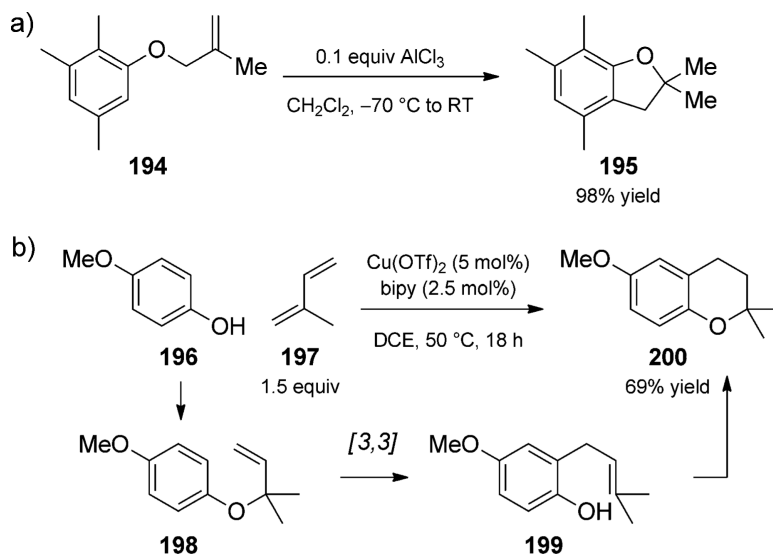
Base-initiated 5-exo-dig cyclization/Claisen rearrangement duets. [Ovaska, 2008, Ref. [59]]

**Scheme 43.**

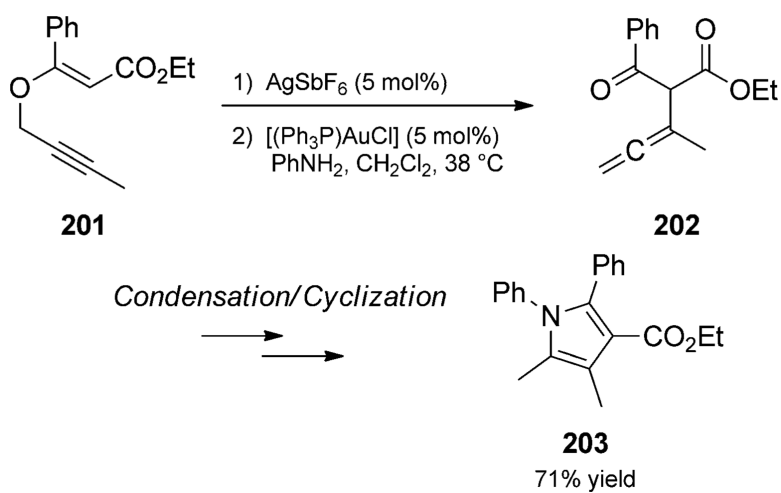
Platinum-catalyzed cycloisomerization/Claisen rearrangement duet. [Yamamoto, **2005**, Ref. [60]]

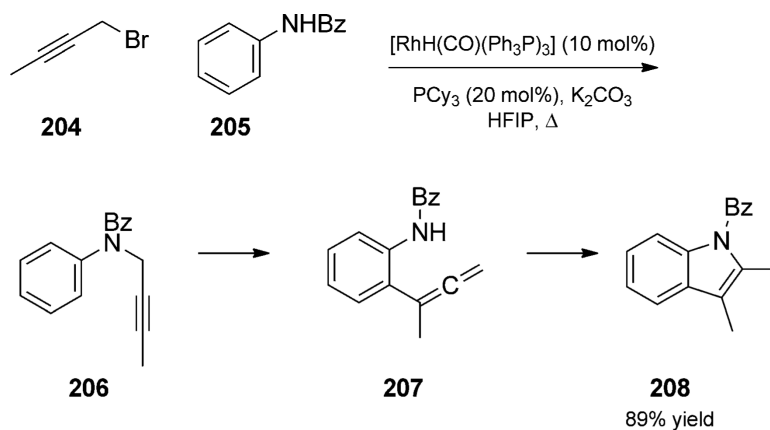
**Scheme 44.**

Rhodium-catalyzed Pauson–Khand/Claisen rearrangement duet. [Chatani, 2010, Ref. [61]]

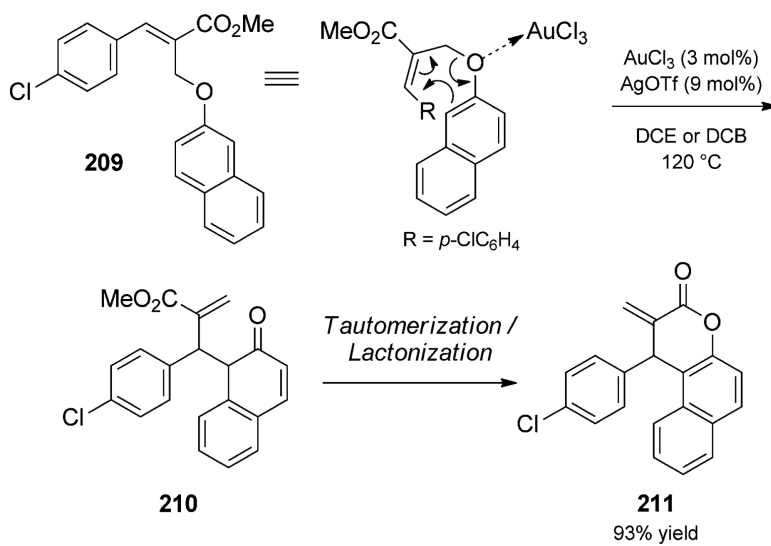
**Scheme 45.**

Lewis acid catalyzed Claisen rearrangement/cyclization (a) duet [Ryu, **1993**, Ref. [62a]] and (b) trio. [Hii, **2008**, Ref. [63a]]

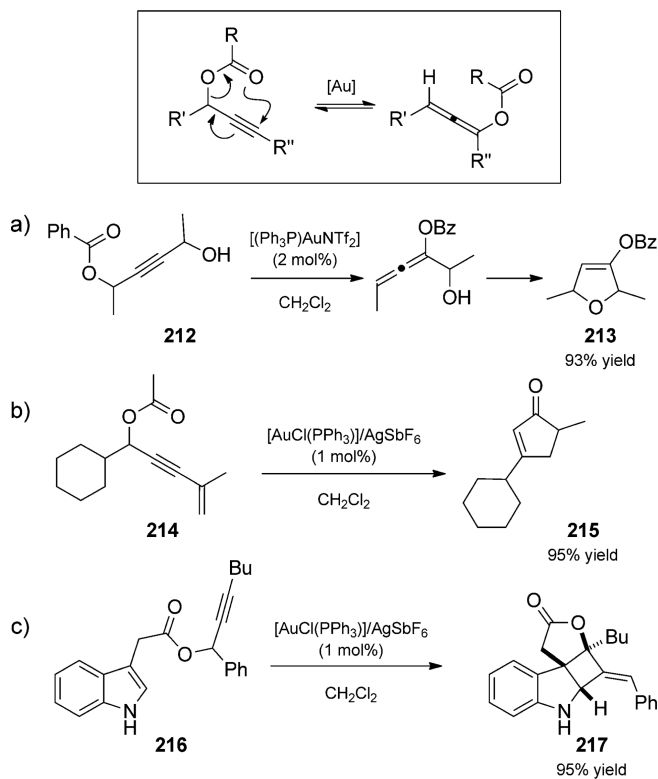
**Scheme 46.**Silver- and gold-catalyzed Claisen trio. [Kirsch, **2006**, Ref. [64]]

**Scheme 47.**

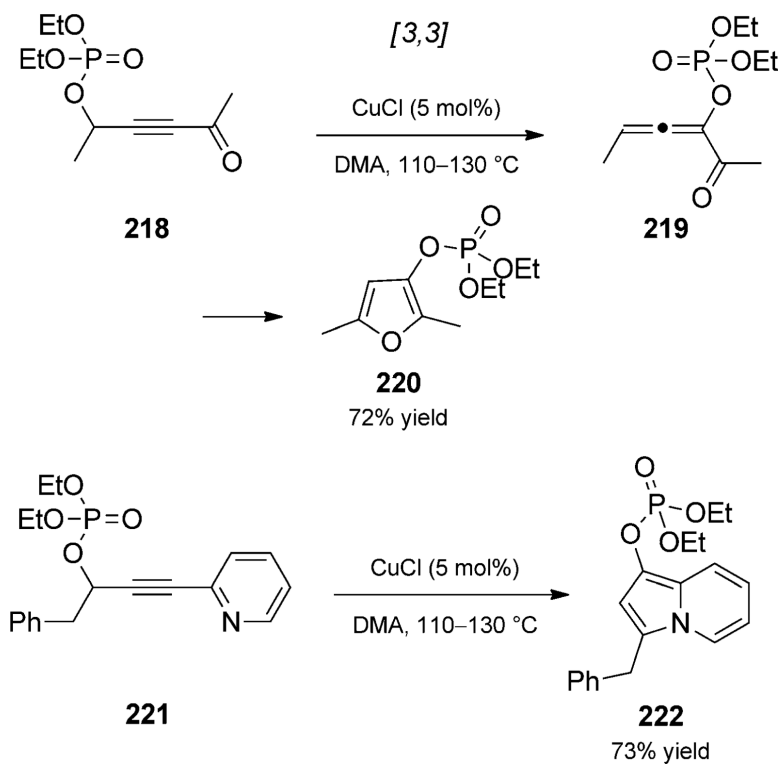
Rhodium-catalyzed one-pot alkylation/amino-Claisen/cyclization trio. HFIP= hexafluoroisopropyl alcohol. [Saito and Hanzawa, **2009**, Ref. [67]]

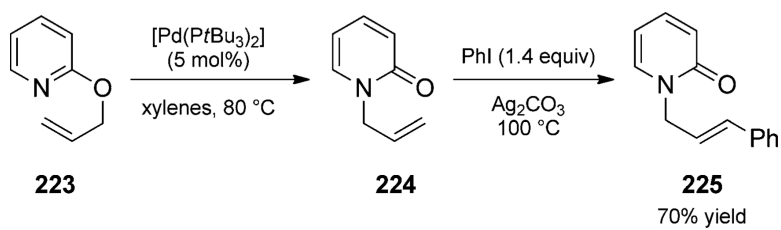
**Scheme 48.**

Gold-/silver-catalyzed Claisen rearrangement/lactonization duet. [Liu and Xu, **2009**, Ref. [68]]

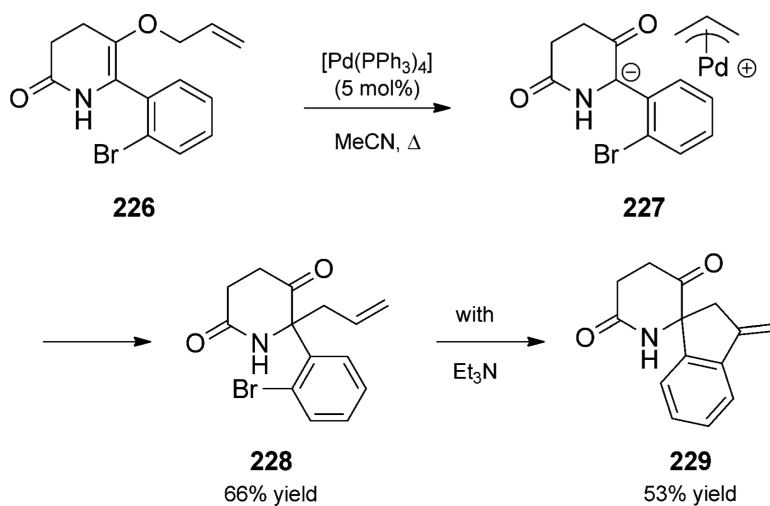
**Scheme 49.**

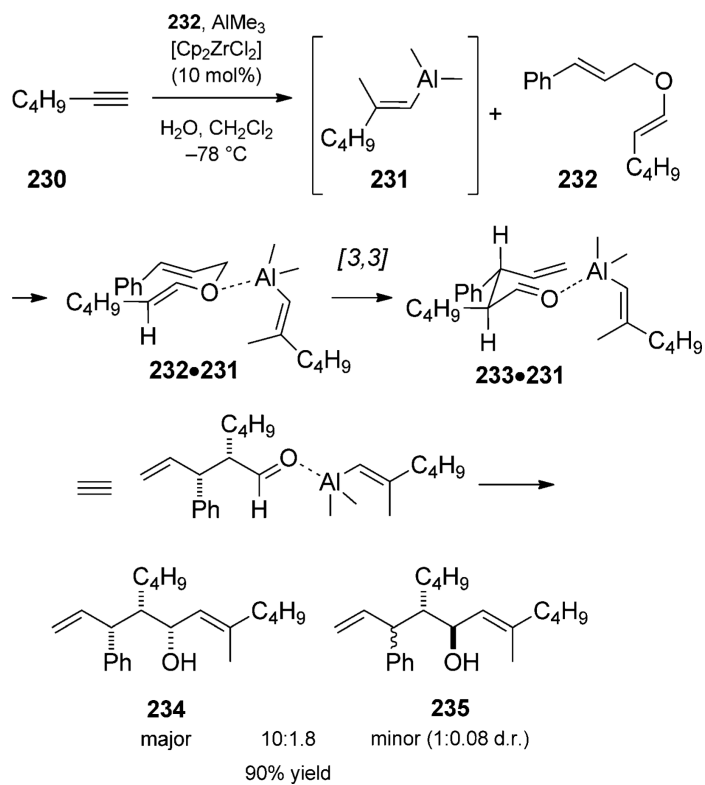
Reaction duets initiated by Claisen rearrangement of propargyl esters. a) [Gagosz, **2006** and related, Shin, **2007**, Ref. [72]], b) and c) [Zhang, **2006/2005**, Ref. [73a,b]]

**Scheme 50.**Cascade [3,3] rearrangement/cycloisomerization duet. [Gevorgyan, **2007**, Ref. [78]]

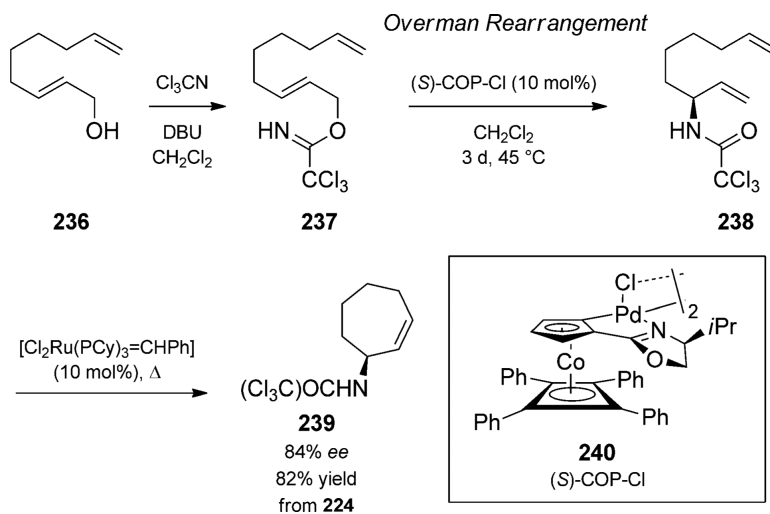
**Scheme 51.**

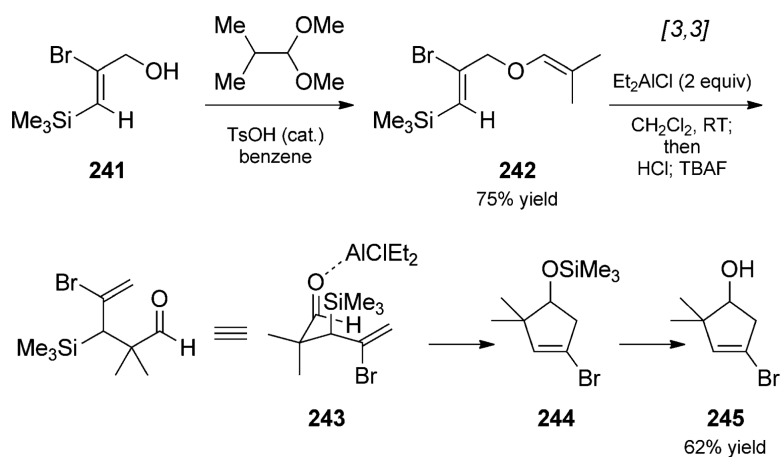
Palladium-catalyzed aza-Claisen/Heck duet. [Itami and Yoshida, 2003, Ref. [79]]

**Scheme 52.**Palladium-catalyzed formal Claisen/Heck duet. [Watson, **1994**, Ref. [80]]

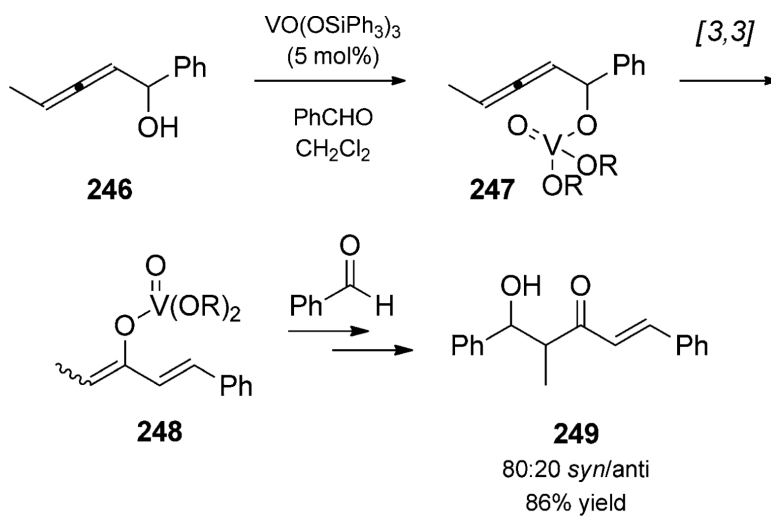
**Scheme 53.**

Zirconium-catalyzed carboalumination coupled with Claisen rearrangement and carbonyl addition, a trio ensemble. [Wipf, **2005**, Ref. [81a]]

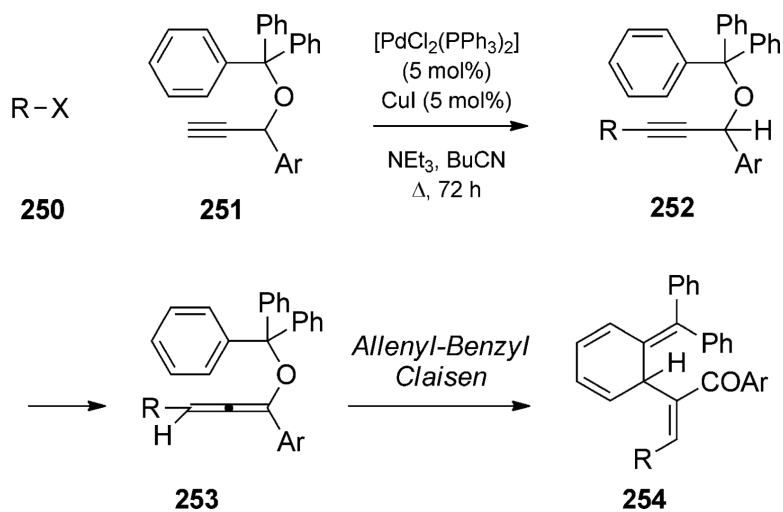
**Scheme 54.**One-pot Overman rearrangement/alkene metathesis duet. [Sutherland, **2009**, Ref. [82a]]

**Scheme 55.**

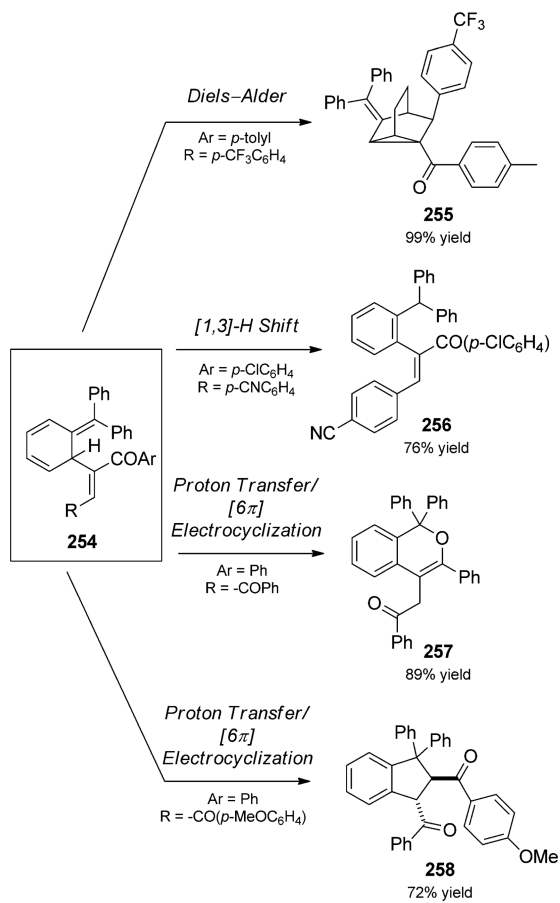
Lewis acid catalyzed Claisen rearrangement/Sakurai allylation duet. [Paquette, **1993**, Ref. [84]]

**Scheme 56.**

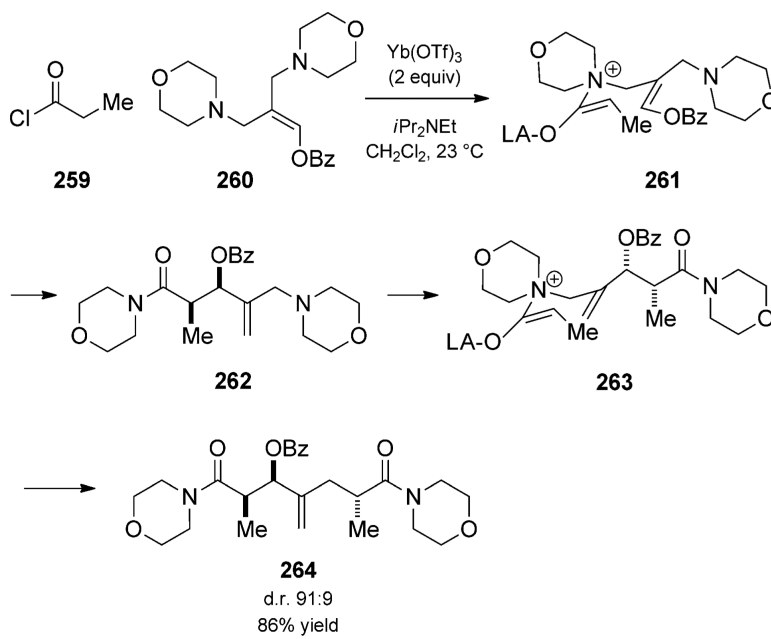
Vanadium-catalyzed allenic alcohol transposition/aldol-type addition duet. [Trost, **2001**, Ref. [86]]

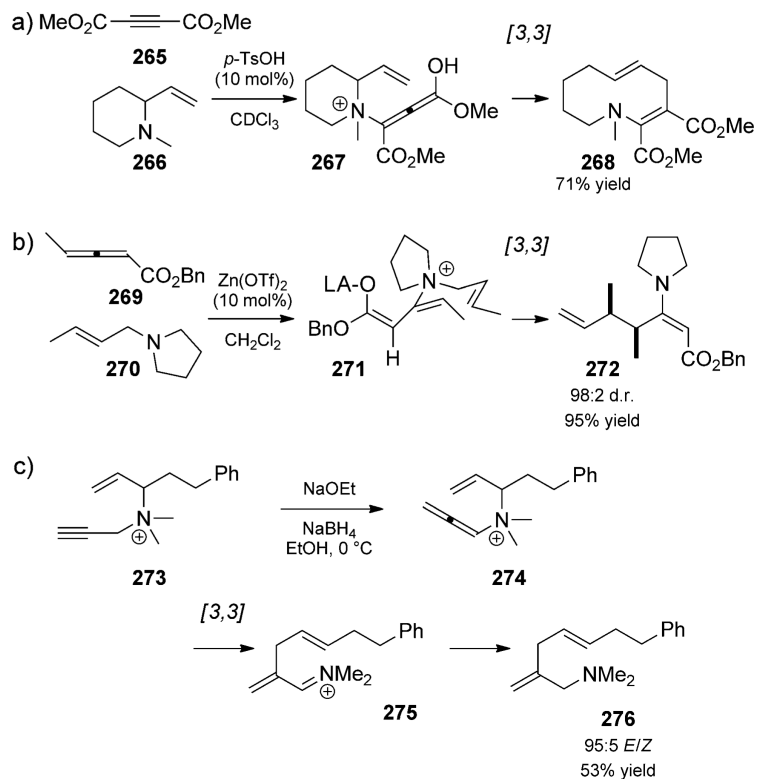
**Scheme 57.**

Palladium-catalyzed coupling/Claisen rearrangement. [Mller, 2006, Ref. [87]]

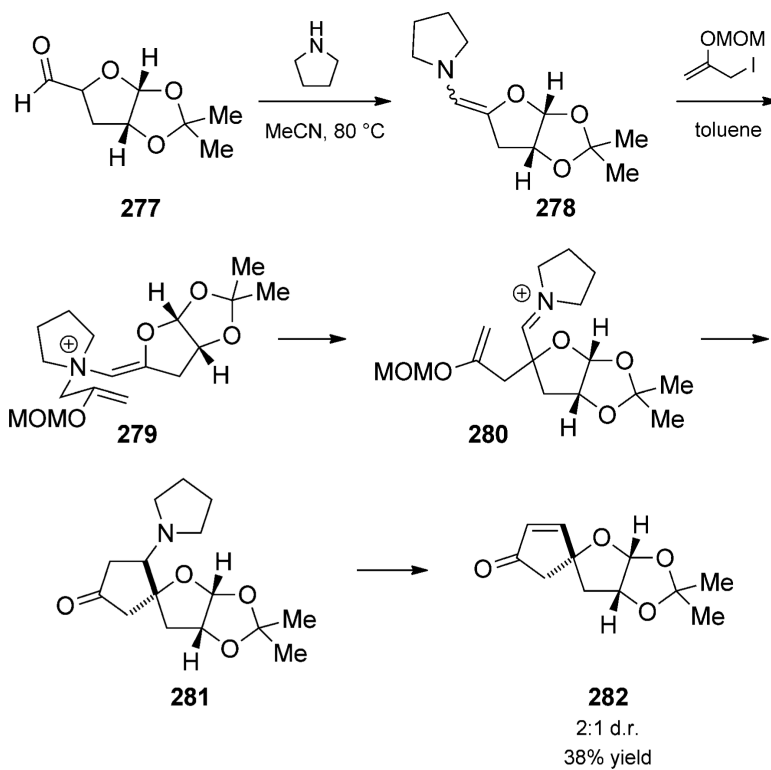
**Scheme 58.**

Pericyclic reaction terminated quartets. [Müller, 2006, Ref. [87]]

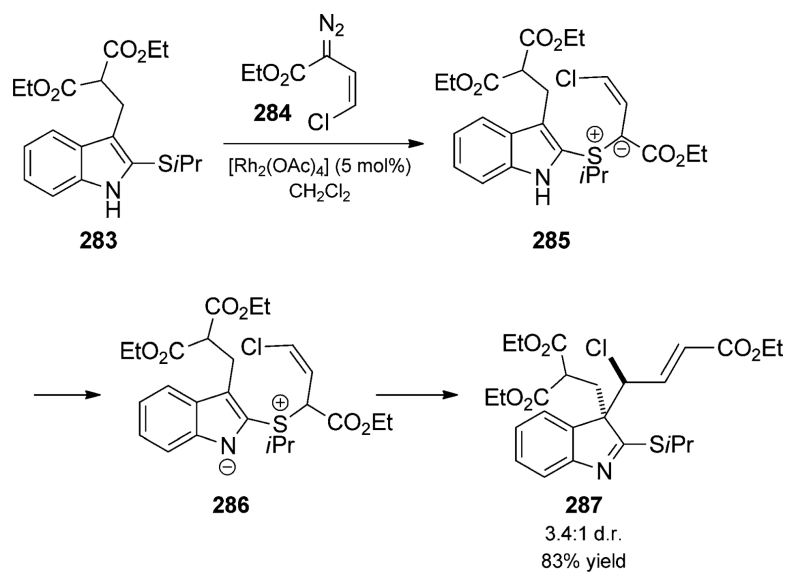
**Scheme 59.**Diastereoselective Bellus–Claisen rearrangement trio. [Macmillan, **2001**, Ref. [90c]]

**Scheme 60.**

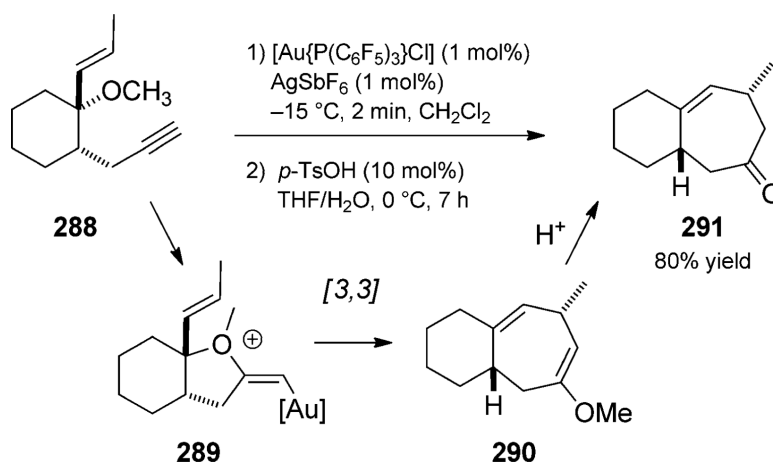
Acid-catalyzed ammonium-Claisen rearrangement duets and a base-mediated isomerization/aza-Claisen/reduction trio. a) [Vedejs, **1994**, Ref. [91]], b) [MacMillan, **2002**, Ref. [90b]], c) [Honda, **2003**, Ref. [92]]

**Scheme 61.**

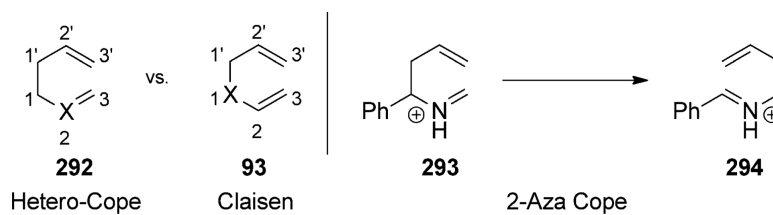
Pyrrolidine-mediated alkylation/cationic aza-Claisen/Mannich rearrangement/elimination quartet. [Florent, **2003**, Ref. [93]]

**Scheme 62.**

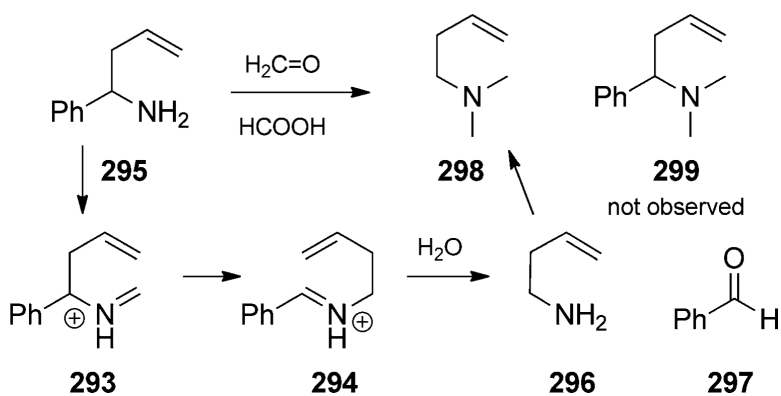
Rhodium-catalyzed ylide formation/thio-Claisen rearrangement duet. [Rainier, **2008**, Ref. [94a]]

**Scheme 63.**

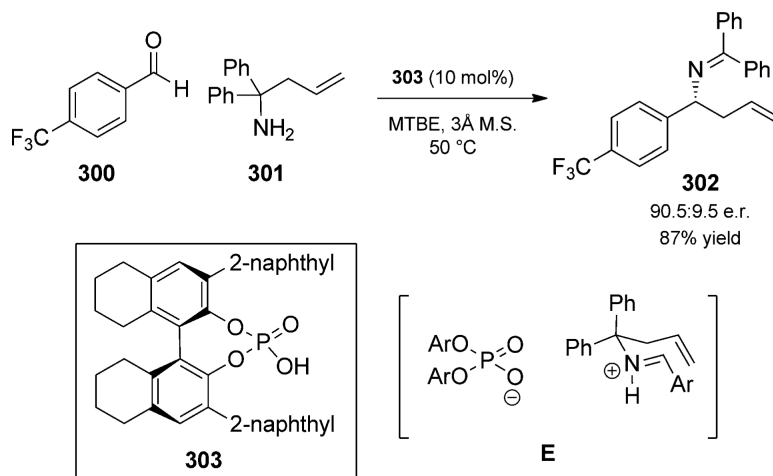
Gold-catalyzed cyclization/[3,3] rearrangement duet. [Rhee, 2008, Ref. [96]]

**Scheme 64.**

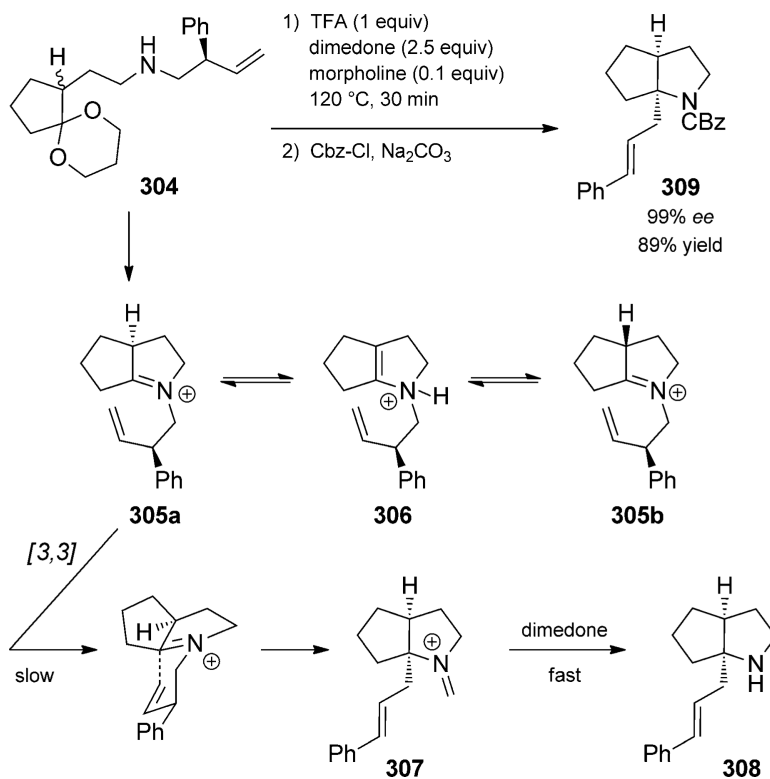
Distinction between hetero-Cope (such as the 2-aza-Cope) and Claisen rearrangement substrates. [Horowitz and Geissman, **1950**, Ref. [97]]

**Scheme 65.**

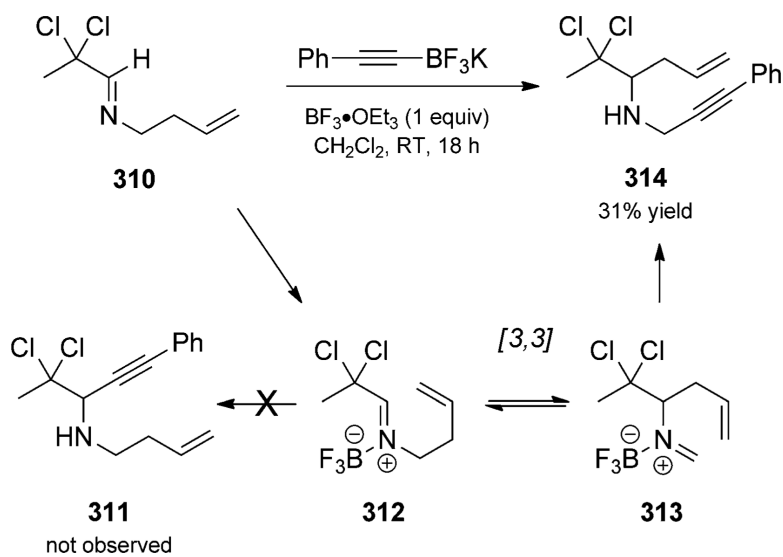
First aza-Cope rearrangement duet. [Horowitz and Geissman, **1950**, Ref. [97]]

**Scheme 66.**

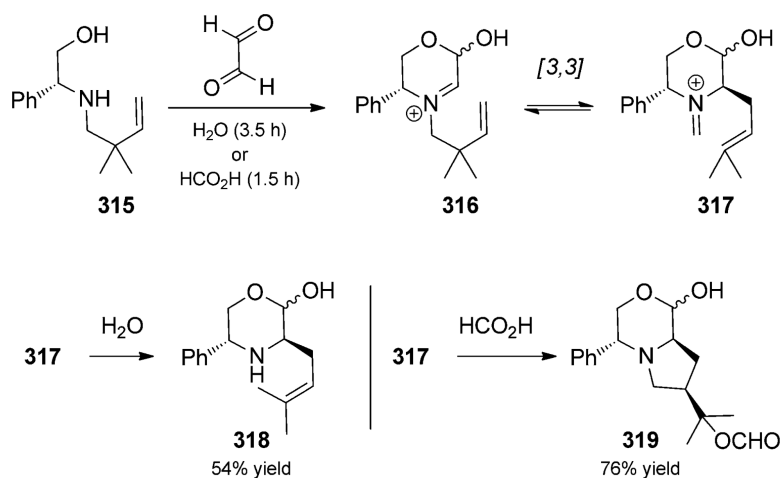
Catalytic asymmetric aza-Cope rearrangement duet. MTBE= methyl tert-butyl ether
[Rueping, **2008**, Ref. [98]]

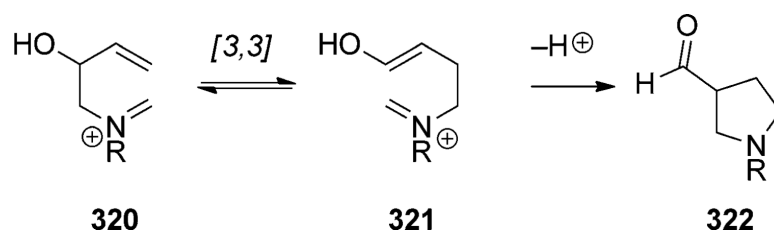
**Scheme 67.**

Dynamic kinetic resolution using an aza-Cope rearrangement quartet. [Overman, **2010**, Ref. [99]]

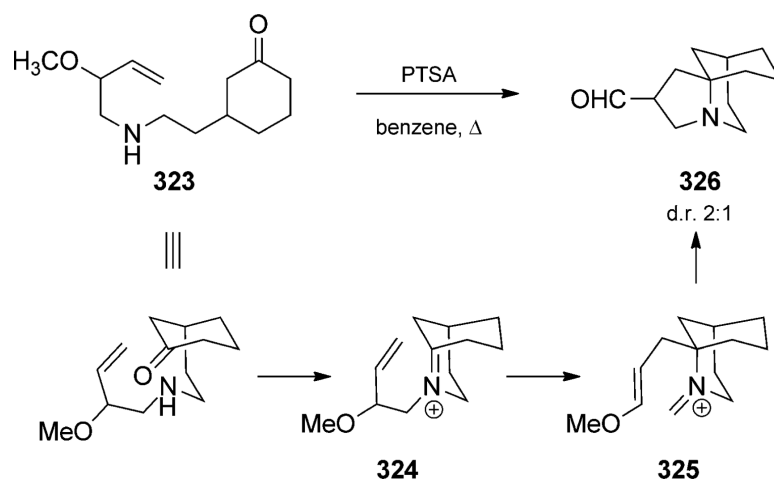
**Scheme 68.**

Lewis acid mediated aza-Cope/Petasis reaction duet. [Tehrani, **2008**, Ref. [100]]

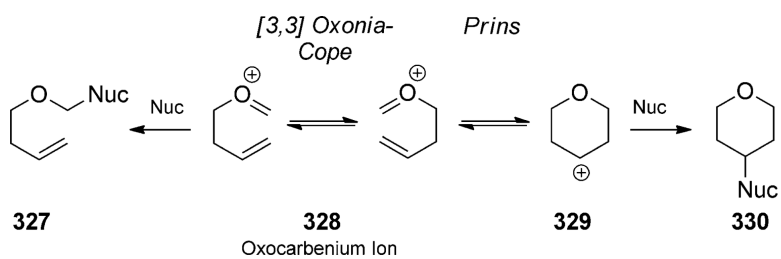
**Scheme 69.**Aza-Cope rearrangements. [Agami, **1992**, Ref. [101]]



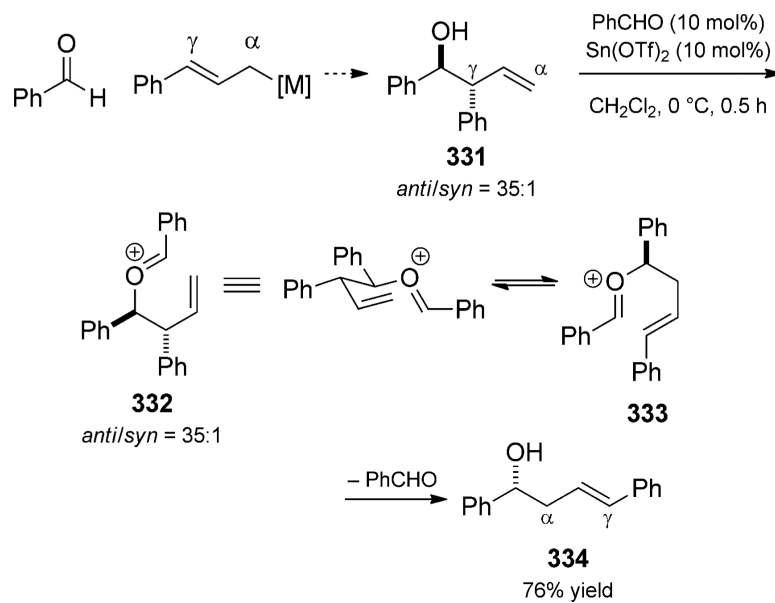
Scheme 70.
Overman's aza-Cope/Mannich reaction duet.

**Scheme 71.**

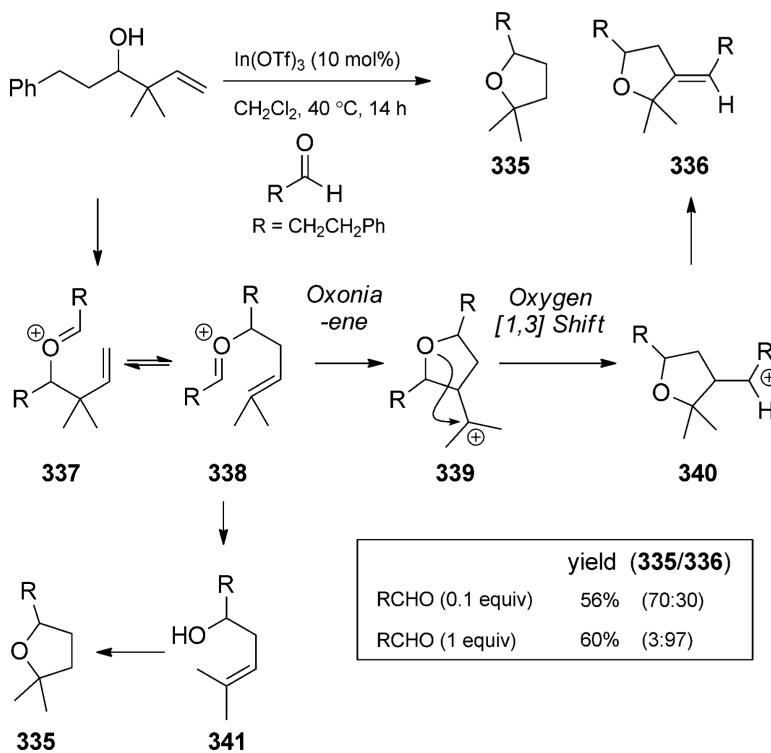
Aza-Cope/Mannich trio via a bridgehead iminium ion intermediate. [Brummond, **2001**, Ref. [105b]]

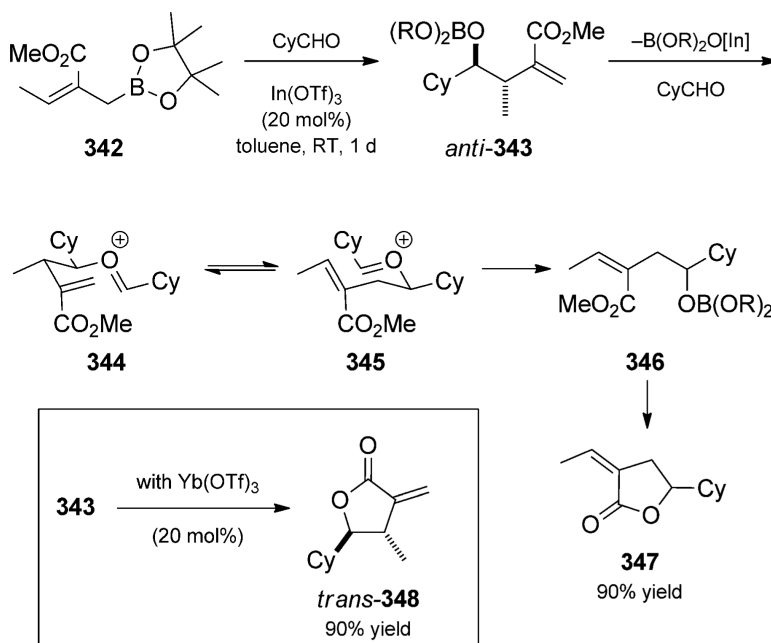


Scheme 72.
Competing oxocarbenium reactions.

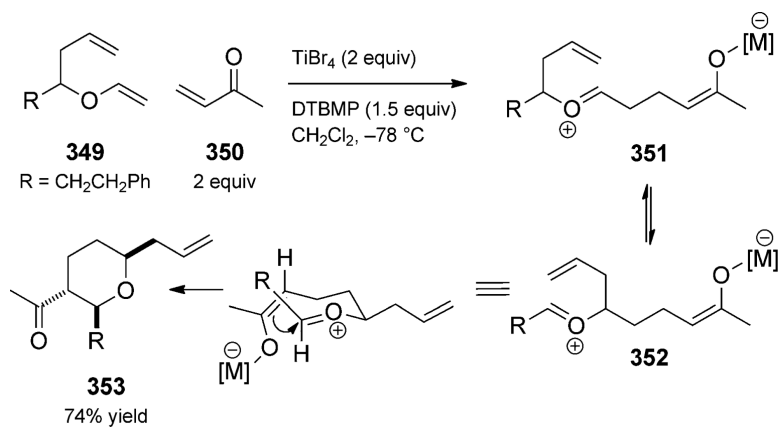
**Scheme 73.**

Isomerization of allylation adducts by oxonia-Cope rearrangement trio. [Nokami, **2000**, Ref. [112a]]

**Scheme 74.**Indium-catalyzed oxonia-Cope/cyclization quartet. [Loh, **2001**, Ref. [113c]]

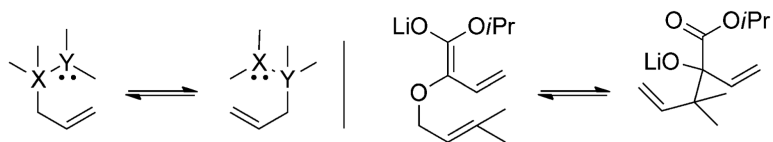
**Scheme 75.**

Indium-catalyzed crotylboration/oxonia-Cope/lactonization trio. [Ramachandran, **2007**, Ref. [116a]]

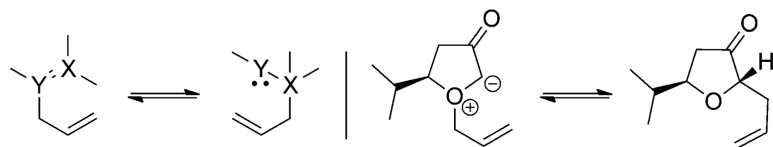
**Scheme 76.**

Titanium-mediated Mukaiyama/oxonia-Cope rearrangement trio. DTBMP= 2,6-di-tert-butyl methyl pyridine. [Rychnovsky, **2005**, Ref. [117]]

a) Type I (e.g. anionic, Wittig rearrangement)

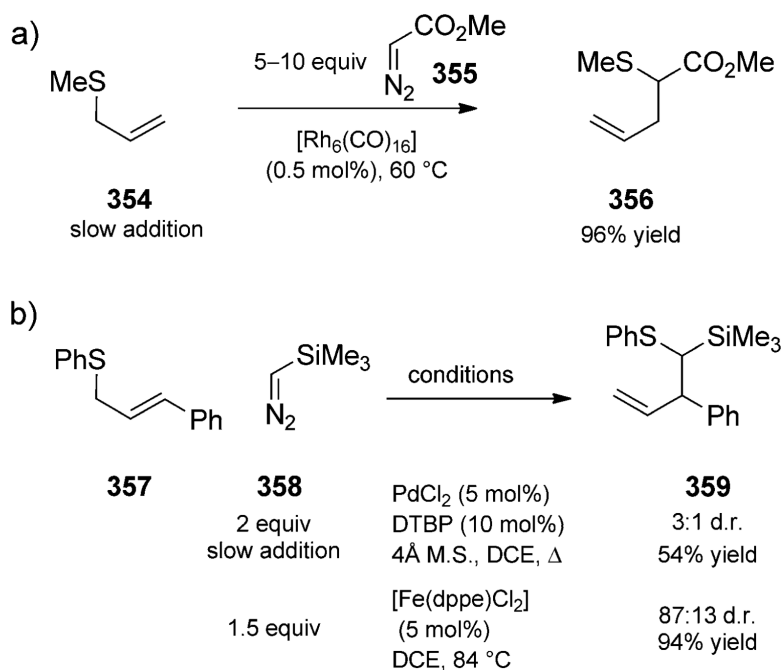


b) Type II (e.g. ylide, Mislow-Evans, carbenic)

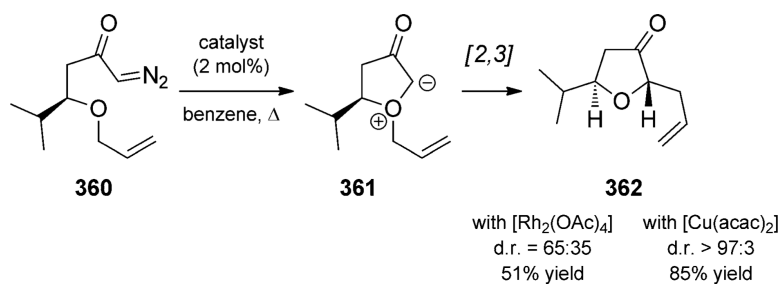


Scheme 77.

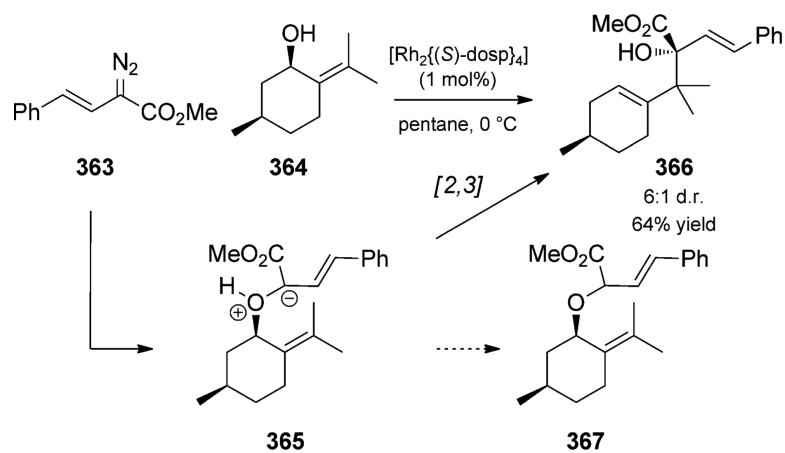
Representative [2,3]-sigmatropic rearrangements. [type I representative: Hiersemann, **2001**, Ref. [121]], type II: Clark, **1992**, Ref. [133]]

**Scheme 78.**

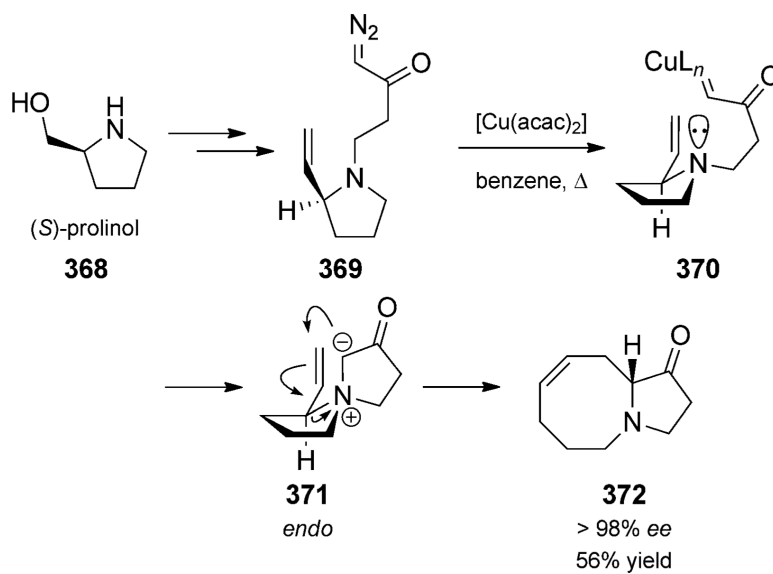
Metal-catalyzed Doyle–Kirmse sulfur ylide duets. dppe = 1,2-bis(diphenylphosphino)ethane. DTBP = 2,6-di-tert-butyl-4-methylpyridine. a) [Doyle, **1981**, Ref. [127]], b) [Van Vranken, **2000/ 2001**, Ref. [128]]

**Scheme 79.**

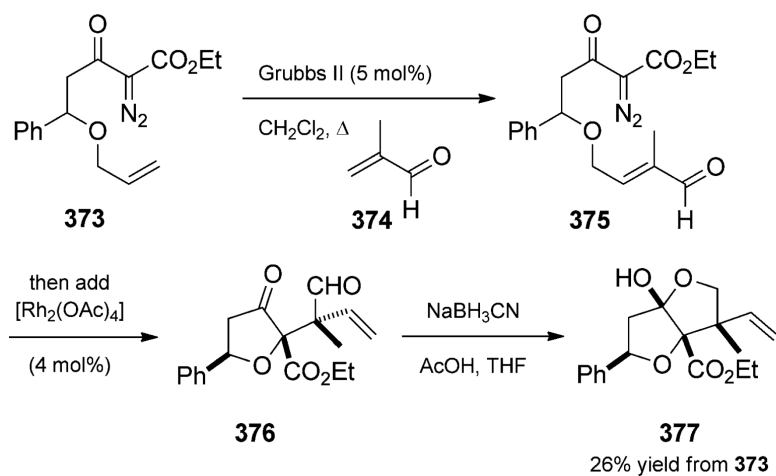
Metal-catalyzed oxonium [2,3] rearrangement duet. [Clark, **1992**, Ref. [133]; for first reports see Pirrung, **1982** and Johnson, **1986**, Ref. [132]]

**Scheme 80.**

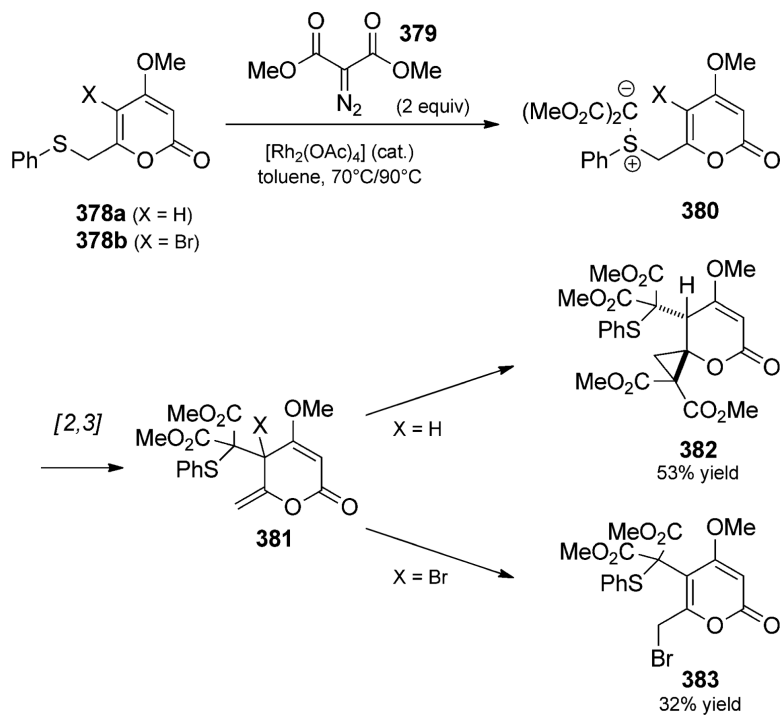
Use of alcohols in ylide formation/[2,3]-sigmatropic rearrangement duet. [Davies, **2010**, Ref. [135]]

**Scheme 81.**

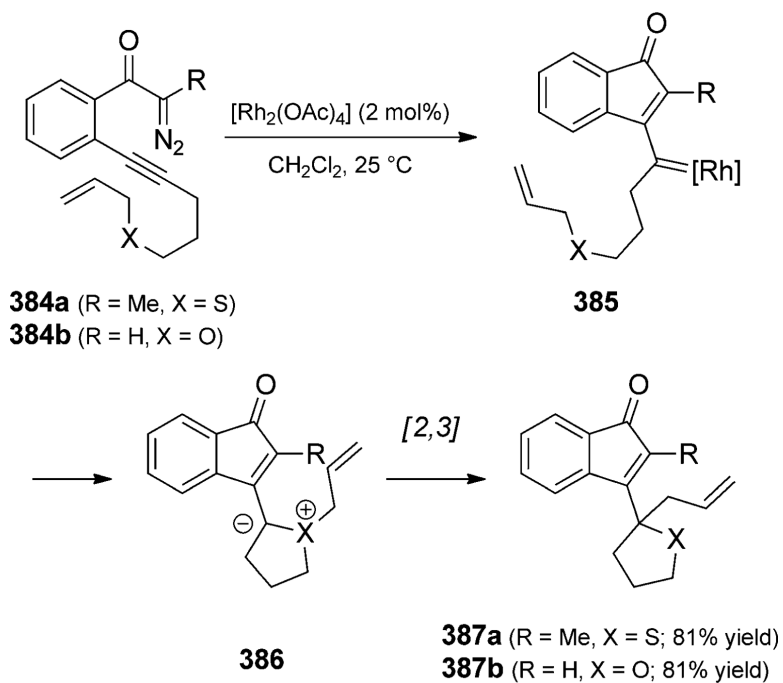
Diastereoselective ammonium ylide formation/[2,3]-sigma-tropic reaction duet. [Clark, 1995, Ref. [136b]]

**Scheme 82.**

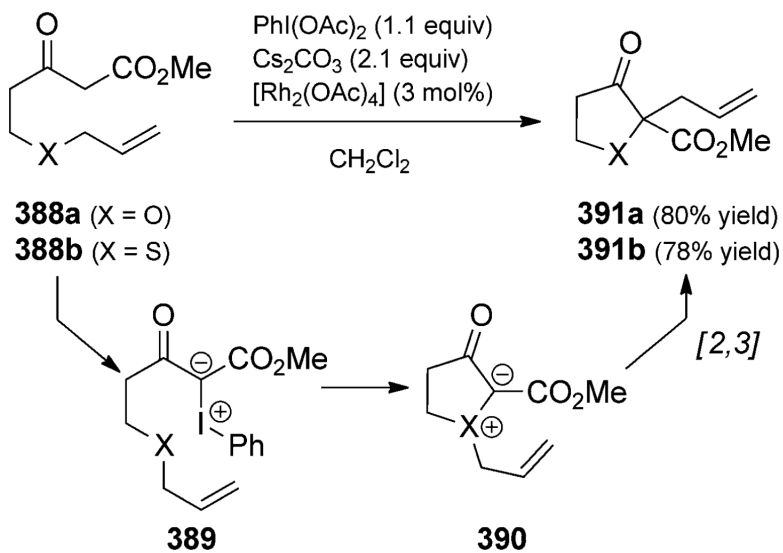
Ruthenium-catalyzed cross-metathesis and rhodium-catalyzed oxonium ylide formation/[2,3]-sigmatropic rearrangement with reduction; a consecutive reaction quartet. [Hodgson, 2008, Ref. [139a]]

**Scheme 83.**

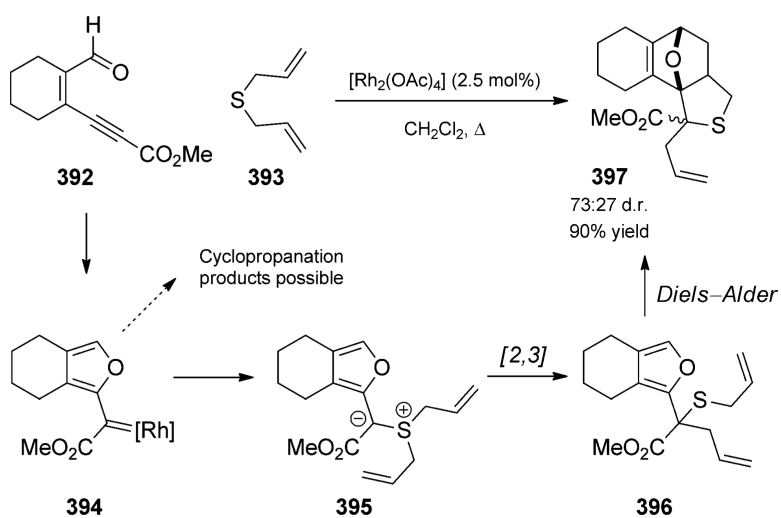
Pyrone reaction trios. [de March and Moreno-MaÇas, **1986/1988**, Ref. [140]]

**Scheme 84.**

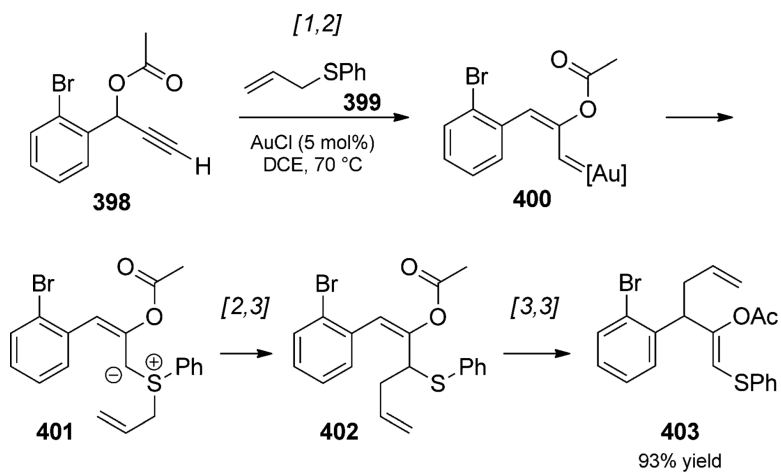
Rhodium-catalyzed alkyne metathesis/[2,3] rearrangement trios. [Padwa, 1995, Ref. [13]; see also Hoye, **1992**, Ref. [141]]

**Scheme 85.**

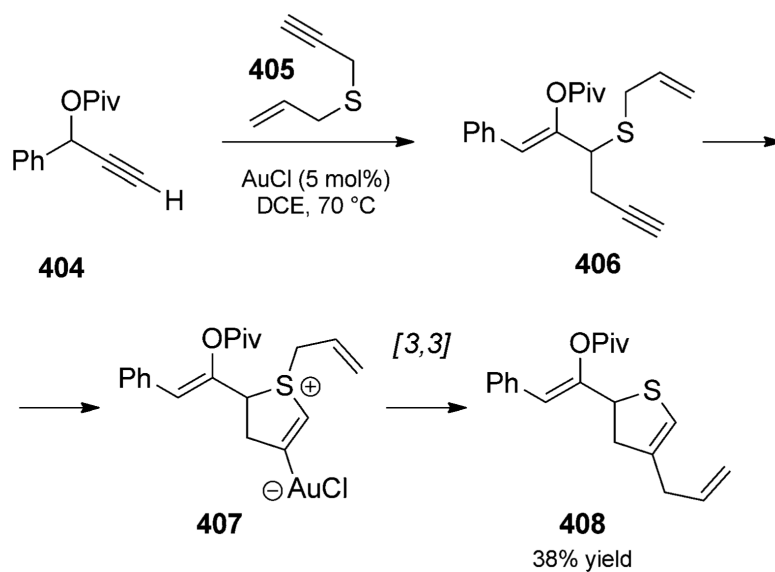
Rhodium-catalyzed ylide formation/[2,3]-sigmatropic rearrangement trio utilizing in situ generation of an iodonium ylide. [West, **2006**, Ref. [142]]

**Scheme 86.**

Rhodium-catalyzed sulfonium ylide quartet. [Ohe and Uemera, **2003**, Ref. [143]]

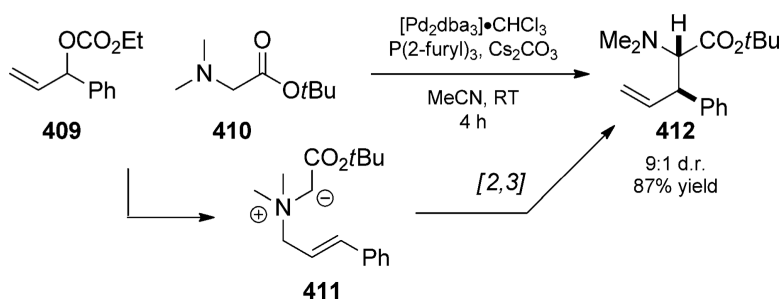
**Scheme 87.**

Gold-catalyzed carbenoid generation/ylide formation/rearrangement quartet. [Davies, **2008**, Ref. [144]]

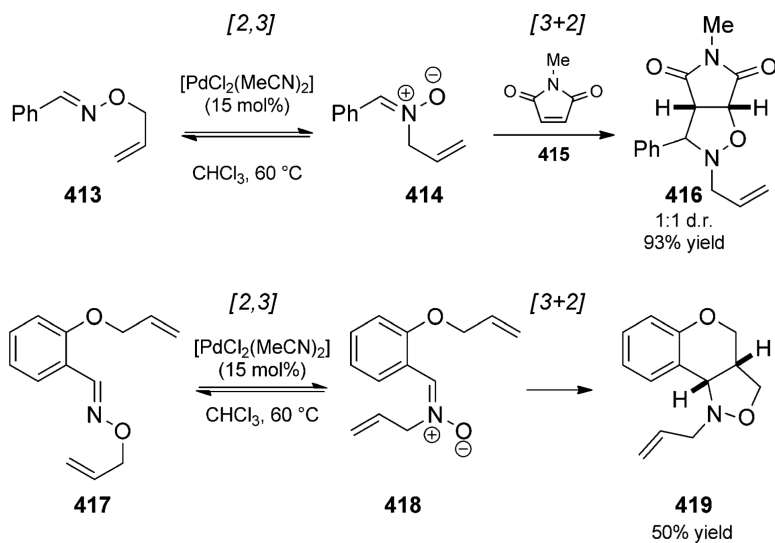
**Scheme 88.**

Alternate gold-catalyzed carbenoid generation/ylide formation/rearrangement quartet.

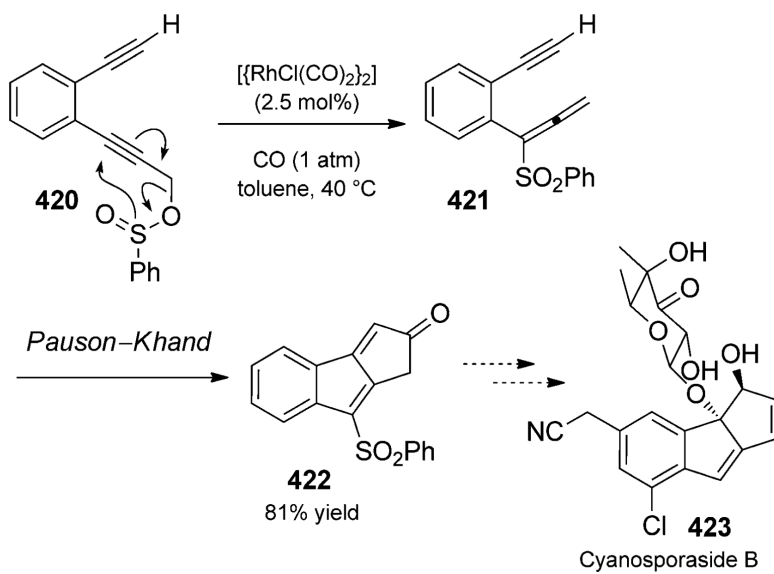
[Davies, **2008**, Ref. [144]]

**Scheme 89.**

Palladium-catalyzed allylic amination/[2,3] rearrangement duet. [Tambar, 2011, Ref. [145]]

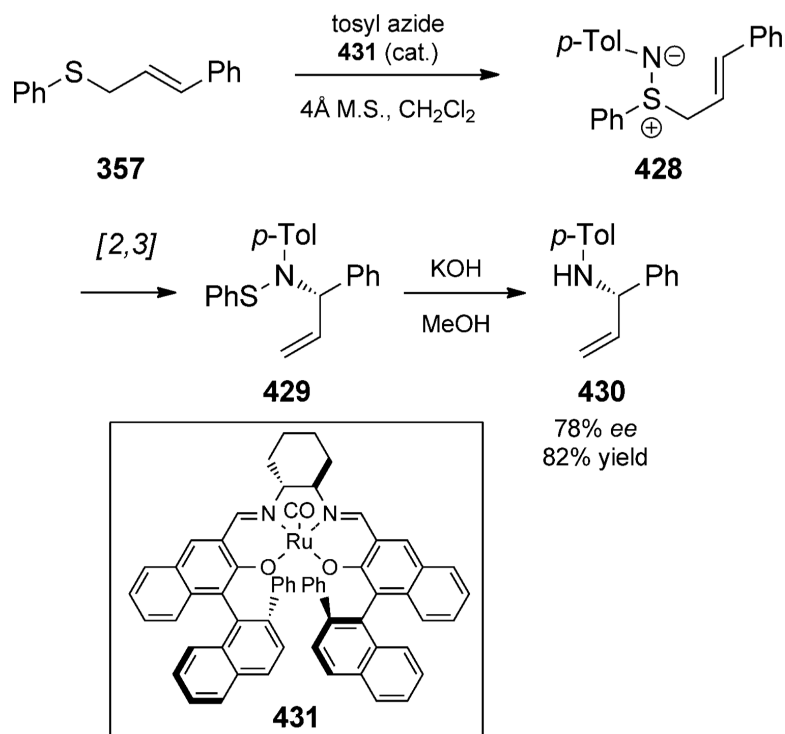
**Scheme 90.**

Palladium-catalyzed reaction duet: a [2,3]-sigmatropic rearrangement/1,3-dipolar cycloaddition. [Grigg, **1991**, Ref. [146]]

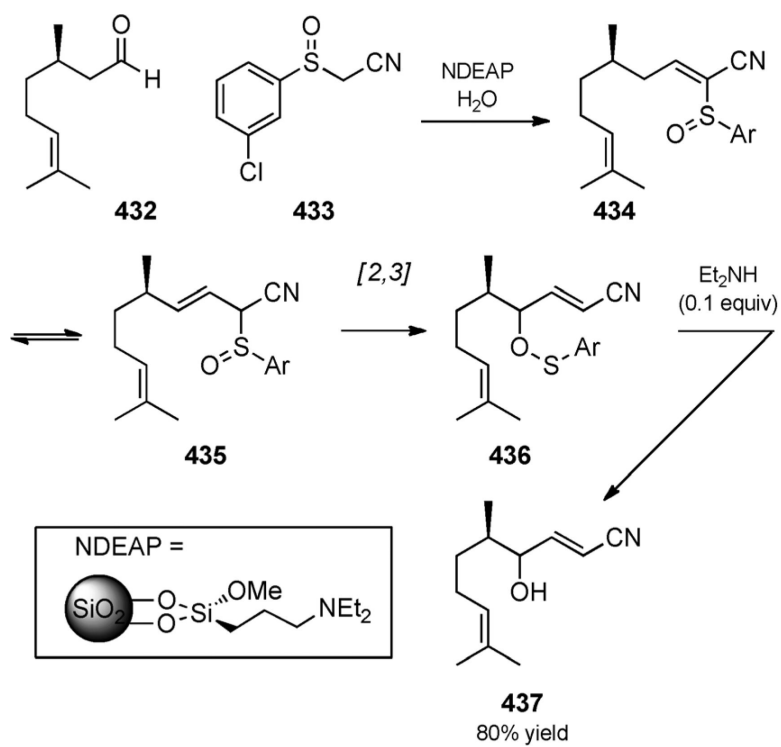
**Scheme 91.**

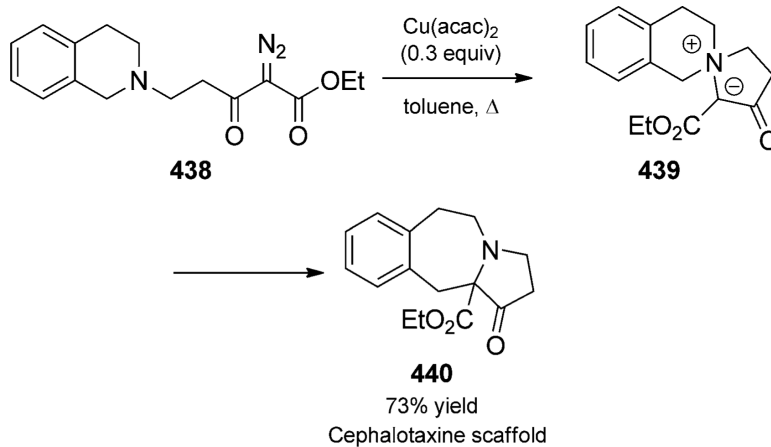
Rhodium-catalyzed [2,3]-sigmatropic rearrangement Pauson–Khand reaction duet. [Mukai, 2009, Ref. [147a]]



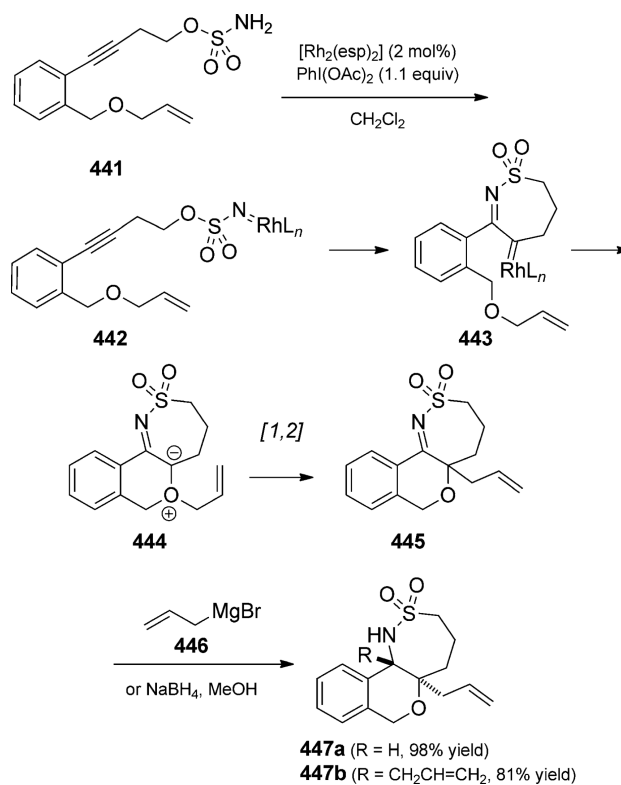
**Scheme 93.**

Ruthenium-catalyzed sulfimidation/[2,3]-sigmatropic reaction trio. [Katsuik, **2002**, Ref. [151]]

**Scheme 94.**Knoevenagel/Mislow–Evans reaction quintet. [Hagiwara, **2006**, Ref. [157]]

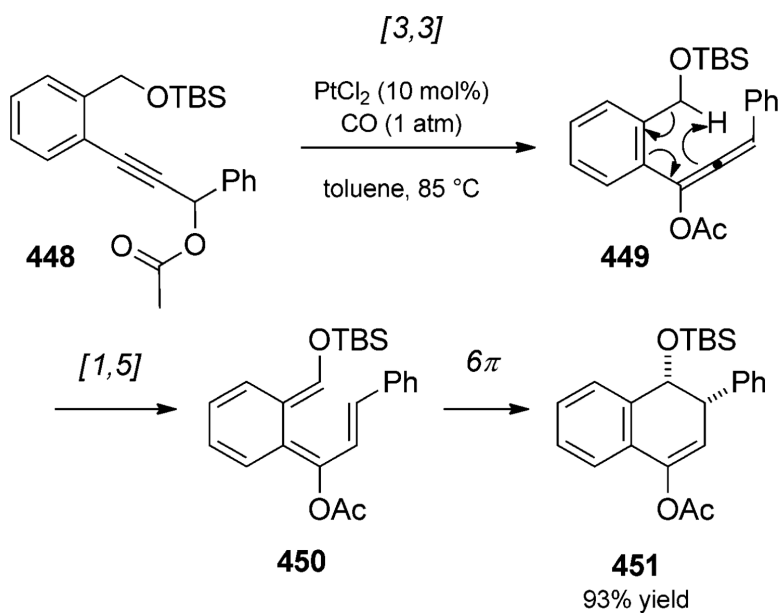
**Scheme 95.**

Padwa's ammonium ylide/[1,2] rearrangement duet. [Padwa, **2001**, Ref. [159]]

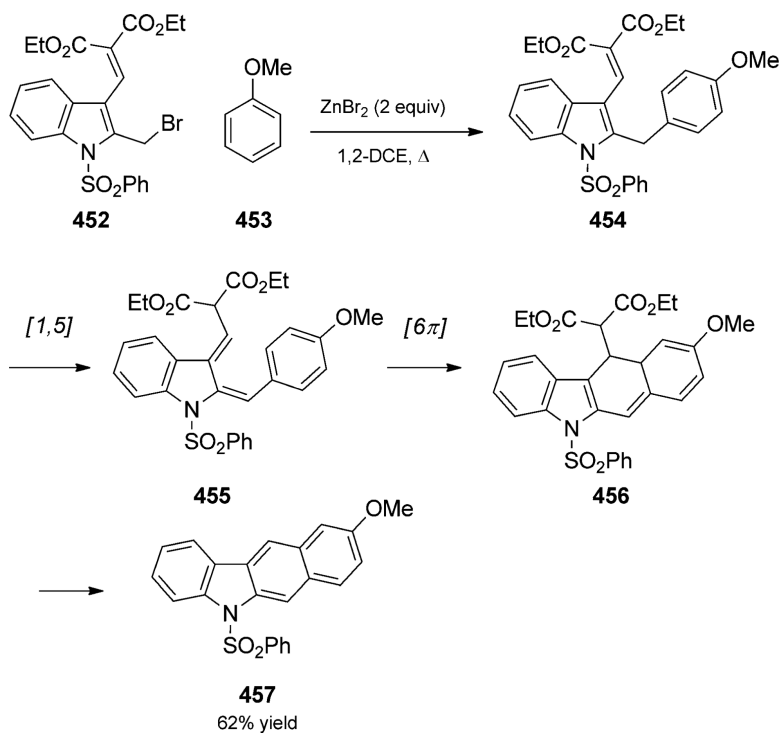
**Scheme 96.**

Rhodium-catalyzed isomerization of metallonitrenes to metallocarbenes; a reaction quartet to efficiently convert simple alkynes to complex bicyclic structures.

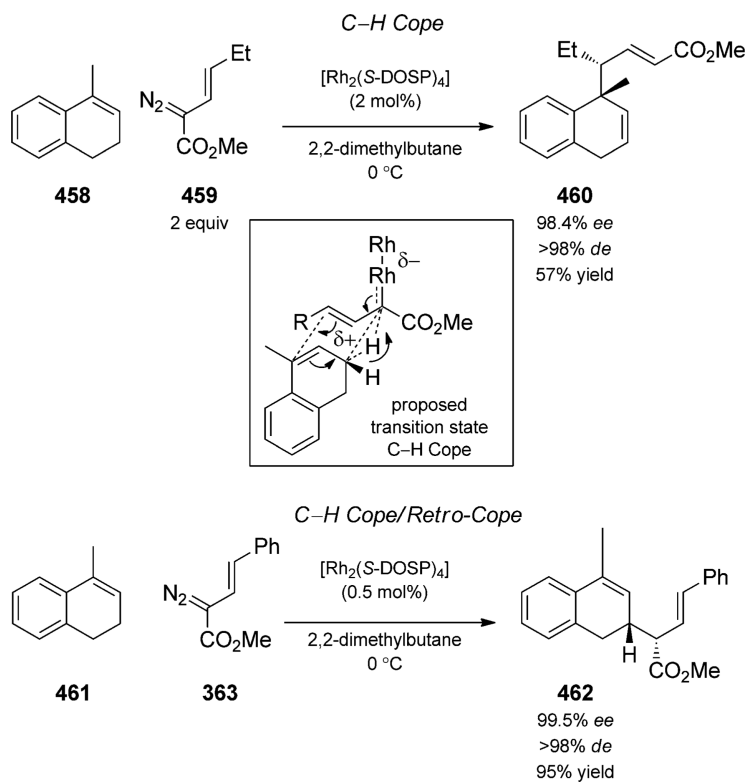
[Rh₂(esp)₂]=Rh₂(a,a,a',a'-tetramethyl-1,3-benzenedipropionate) [Blakey, **2008**, Ref. [160]]

**Scheme 97.**

Platinum-catalyzed [1,5]-H-shift reaction. [Liang, 2008, Ref. [161]]

**Scheme 98.**

Zinc(II)-mediated arylation/sigmatropic rearrangement trio. [Mohanakrishnan, **2009**, Ref. [162]]

**Scheme 99.**

Rhodium-catalyzed C-H activation Cope rearrangement and C-H activation Cope/retro-Cope rearrangement duet. [Davies, 2004, Ref. [163b]]